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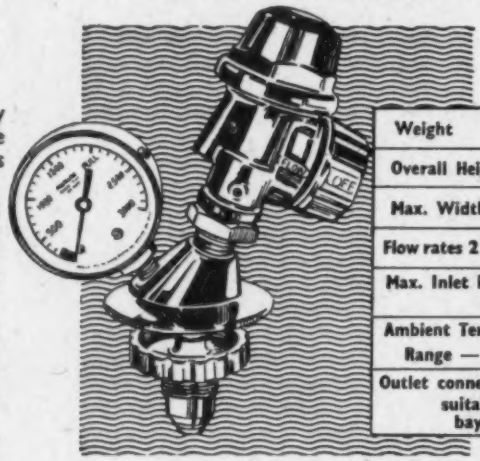

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BRITISH MEDICAL JOURNAL

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BLOOD-GROUP ANTIBODIES AND RED-CELL DESTRUCTION*

BY

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In founding these lectures Dr. George Oliver not only wished to record his admiration for Professor William Sharpey—"the Founder of English Physiology"—but also intended "to promote physiological knowledge by observation and experiment, and to encourage the application of physiological knowledge to the prevention and cure of disease and the prolongation of life."

The study of blood transfusion in man has complied with some of these intentions, for it has led not only to knowledge of how to transfuse blood from one person to another without ill effects, but has also contributed in many ways to knowledge of physiological and pathological processes. For example, it was through the study of the survival of transfused red cells that the first correct estimates of red-cell life-span in man were obtained, and haemolytic anaemias were first divided into those due to an intrinsic red-cell defect and those due to a random destructive process.

The safety of blood transfusion depends very largely on the avoidance of serological incompatibility, and a detailed consideration of this problem forms the main subject of these lectures. In pursuing this problem a certain amount of new information about haemolytic processes has been obtained, and this will also be discussed.

I should like to begin by tracing the history of the idea that serological compatibility is essential to safe and effective transfusion: then to discuss the discovery of human blood groups and to consider briefly some of the characteristics displayed by blood group antibodies *in vitro*. Next I shall consider methods of estimating the survival of incompatible red cells *in vivo*, and discuss particularly the information that can be obtained using ^{51}Cr as a label. In the second lecture I shall consider how far results observed *in vivo*, when red cells are transfused, can be predicted from tests made beforehand *in vitro*.

The First Two Hundred Years of Blood Transfusion

The first successful cross-transfusion experiments were performed between dogs by Dr. Richard Lower (1665–6). His command of technique was impressive. He was able, by using a large dog (a "mastive") as a donor and a little dog (a "curr") as a recipient, to pass through the recipient an amount of blood equal to twice its total blood volume, and to control the transfusion so well that the recipient left the table in excellent condition: "After he was unty'd he ran away and shak'd himself as if he had been thrown into water." Serological incompatibility did not intrude in these particular experiments, since severe incompatibility in first transfusions in dogs is virtually unknown (Dr. Scott Swisher, personal communication).

Shortly after Lower had carried out his first successful transfusion, the first transfusion to a human was carried out by Denis (1667–8) in France, using lamb's blood. He performed several transfusions, using either a lamb or a calf as a donor, and some of these transfusions were accompanied by severe reactions: "As this second Transfusion was larger, so were the effects of it quicker and more considerable. As soon as the blood began to enter into his veins, he felt the like heat along his Arm and under his Arm-pits which he had felt before. His pulse rose presently, and soon after we observed a plentiful sweat over all his face. His pulse varied extremely at this instant, and he complain'd of great pains in his Kidneys, and that he was not well in his stomack, and that he was ready to choak unless they gave him his liberty." The following morning: "He made a great glass full of Urine, of a colour as black, as if it had been mixed with the soot of chimneys."

Shortly after this, transfusion was placed under an interdict in France, and little more is heard until the nineteenth century. Then Dr. Blundell, of the United Hospitals of St. Thomas and Guy, began to experiment with the injection of human blood into dogs. He found that a dog which had been bled could be revived by a transfusion of dog's blood, but that the transfusion to a dog of as little as 4 oz. (114 ml.) of human blood could be fatal (Blundell, 1824). Blundell, now convinced that only human blood was suitable for transfusion to humans, began very cautiously experimenting in man, usually not daring to attempt transfusion until his patient was beyond hope. Finally, he recorded a successful case in which 8 oz. (227 ml.) had been transfused by means of a special syringe, "the impellor" (Blundell, 1828–9).

By 1873 about 240 transfusions of all kinds had been given in England, according to Jennings (1883); in most of these it is probable that relatively small volumes of blood had been injected from some form of syringe.

Aveling (1873) carried out some cross-transfusions, inserting a cannula into the arm vein of the donor, connecting this to a small length of rubber tubing with a bulb, and then to a cannula in the arm vein of the recipient. Aveling's very first case—according to him only the fifth cross-transfusion ever performed in England—was a great success, and is recorded in a

*The first of two Oliver-Sharpey Lectures given at the Royal College of Physicians of London on March 10 and 12, 1959.

well-known picture, showing the family coachman acting as donor to the lady of the house.

Despite Blundell's earlier work, Aveling now turned to the use of lambs as donors, and published a case in which he had cross-transfused a few ounces of lamb's blood (Aveling, 1874). The transfusion was not a success, but this did not stop Aveling from recommending that when human blood was unobtainable one should use lamb's blood without hesitation: "No person should now be allowed to perish from loss of blood without transfusion in some form or other being attempted."

Discovery of Serological Incompatibility

Meanwhile very important progress was being made in Germany. Landois (1875) discovered that when the red cells of one animal were mixed with the serum of another animal and incubated at 37° C. they might be lysed within two minutes. At about the same time Professor Ponfick, of Rostock, reported the results of cross-transfusion between animals of many species. In all, 16 combinations of donor and recipient were tried. He found that when donor and recipient belonged to the same species as much as 60 ml./kg. of blood could safely be given, but that when they were of different species the transfusion of as little as 4 ml./kg. might be fatal. He also found that animals transfused with the blood of another species developed haemoglobinuria, not haematuria as had previously been supposed. He further showed that if blood was haemolysed *in vitro* by freezing and thawing and then injected into an animal of the same species haemoglobinuria could also be produced. Moreover, the amount of lysed blood which would produce haemoglobinuria (about 1.2 ml./kg. of the recipient's body weight) was almost exactly the same as the amount of intact blood of a foreign species which would produce haemoglobinuria (Ponfick, 1875).

Thus, by 1875 it was clear that when the blood of one species was transfused to another the donor's cells were promptly lysed by the serum of the recipient. Despite this, some people continued to be enthusiastic advocates of lamb's blood, and in the textbook of medicine (Fagge and Pye-Smith, 1891) which my father used at Guy's at the turn of the century it was felt necessary to emphasize that in transfusion only human blood should be used.

Discovery of the ABO Blood-group System

It is interesting that Sharpey's pupil, E. A. Schäfer, came somewhere near discovering the existence of serological incompatibility between human bloods, for in 1880 he published a paper in which he described the lysis of human red cells when mixed with animal serum. Had he carried out tests between a few samples of human red cells and a few samples of human serum he would certainly have found agglutination in some of the mixtures.

This discovery, however, remained for Landsteiner to make. In the account which he published in 1901 he made it clear that he fully understood the significance of his discovery and its relevance to blood transfusion.

Landsteiner occupies a unique place in the field of blood groups: for the 40 years after his discovery of the ABO system he continued, with various colleagues, to make most of the important discoveries in the field. At the same time, of course, he made other contributions to immunology of the greatest importance. After qualifying as a doctor in 1891 he had had five years' training as a chemist, and thus equipped himself for the contributions he was to make on the nature of serological specificity.

After the publication of Landsteiner's discovery of the blood groups many years elapsed before the idea of matching blood before transfusion was accepted. In 1909 Crile, in his book on transfusion, wrote, "In the author's opinion agglutination may be disregarded." Ottenberg and Kaliski (1913) were among the first to advocate cross-matching, but even they were inclined to underestimate the significance of agglutination *in vitro*, as opposed to haemolysis.

One may well wonder why there were not more accidents. One reason is that if transfusions are given between humans without any preliminary tests whatever only one out of three will be incompatible (see Table I). Moreover, even when blood of the wrong ABO group is transfused the outcome will seldom be fatal, and may even appear to be favourable. For example, in one case reported elsewhere a patient of group A was admitted to hospital suffering from melaena; her haemoglobin concentration was 5 g./100 ml. and her pulse was thready. Immediate transfusion seemed desirable, and the blood of two donors was cross-matched by a house-physician. The donor blood was of group B, but the patient rapidly improved during the transfusion. Subsequent tests showed that the anti-B in the recipient's serum was completely absorbed by the transfusion (of 1,000 ml. of group B blood), and that the bulk of the injected cells survived normally for five days after transfusion. There was then an immune reaction, and the transfused cells were eliminated. However, this produced only a mild jaundice, and a fall in haemoglobin concentration which the recipient was now well able to tolerate (Mollison, 1956, p. 345).

If all the other blood-group systems were ignored in transfusion their antibodies would cause trouble only very seldom. Some examples of the approximate risks involved are given in Table II. Thus the risk of incompatibility from anti-Le^a if no tests were made would be 1 in 1,000, and the risk from anti-Rh would be similar. Probably not more than 1 in 5 or 1 in 10 of such incompatible transfusions would cause a serious haemolytic reaction. Some antibodies, such as anti-Wr^a, occur relatively commonly in human sera, but the

TABLE I.—*Chance of Giving Incompatible Blood if ABO Groups of Donor and Recipient are Ignored in Transfusion*

Recipient's Blood Group	Blood Groups of Incompatible Donors		Chance of Incompatible Transfusion
	(i) Frequency	(ii) Combined Frequencies of Donors	(i) × (ii)
O	0·47	A, B, AB	0·53	0·25
A	0·42	B, AB	0·11	0·05
B	0·08	A, AB	0·45	0·04
AB	0·03	None	0	0
				0·34

TABLE II.—*Risk of Incompatibility from Some Antigens Outside the ABO System*

	Frequency of:		Risk
	(i) Antigen	(ii) Corresponding Antibody	(i) × (ii)
Le^a	0·2	0·005	0·001
Rh (D)	0·8	0·001	<0·001
Wr^a	0·002	0·01	0·00002

corresponding antigen is very infrequent, so that the risk of an incompatible transfusion is minute.

Discovery of Other Blood-group Systems

The way in which the various blood-group systems were discovered is summarized in Table III. After the discovery of the ABO system in 1901 no new blood-group systems were found for 25 years. Landsteiner

TABLE III.—*Subjects in Which the Antibodies of the Eleven Main Blood-group Systems Were First Found*

Blood-group Systems	Antibodies First Found in
ABO, Le	Normal subjects
MN, P	Rabbits injected with human red cells
Rh	Rabbits injected with rhesus monkey red cells
Rh, K, Jk, Di	Mothers of infants with haemolytic disease
Lu, Fy, Js	Transfused patients

examined human sera for other antibodies, but could find only weak agglutinins, active at low temperatures. It occurred to Landsteiner and Levine that they might be able to reveal other antigens in human red cells by making immune antibodies against them in rabbits, and accordingly they carried out experiments in which several different samples of human red cells were injected into rabbits. Antibodies identifying these new human antigens were obtained (Landsteiner and Levine, 1928), and to the first of these the letter M was given, to show that the antigen had been identified with immune serum—the letter I was avoided because of possible confusion with the numeral 1 (Levine, 1944).

Landsteiner and Wiener (1941) adopted a slightly different approach when they injected the red cells of rhesus monkeys into rabbits. They hoped that in this way they might reveal the existence of an antigen present both in human cells and in rhesus cells, and they were successful. At about the same time Levine and his colleagues were making their highly important discoveries relating to iso-immunization in pregnancy. Levine and Stetson (1939) had found an antibody in the serum of a recently delivered woman whose foetus had died *in utero*. They discussed the possibility that the mother had been immunized by cells of her foetus which carried an antigen inherited from the father that was foreign to the mother. This was the beginning of the fascinating work which led to the discovery that iso-immunization in pregnancy is the usual cause of haemolytic disease of the newborn (Levine *et al.*, 1941).

"Incomplete" Blood-group Antibodies

Anti-Rh differs from anti-A and anti-B in being more difficult to detect *in vitro*. In many cases a serum containing Rh antibody fails to agglutinate Rh-positive red cells suspended in saline. Race (1944) and Wiener (1944) independently discovered one method of demonstrating these "incomplete" types of antibody, and in the ensuing few years many other methods were described. Certainly the most important of all these methods was the antiglobulin test (Coombs, Mourant, and Race, 1945), which is discussed in some detail later. By means of the indirect antiglobulin test several more blood-group systems were discovered—for example, K, Jk, and Fy. In some cases the antibodies were first found in the serum of a mother whose infant had had haemolytic disease of the newborn, or were found attached to the red cells of the infant; in other cases they were found in the serum of a patient who had received transfusions and so been immunized.

Complement-binding Blood-group Antibodies

Coombs and Mourant (1947) showed that the reaction between an anti-human-globulin serum and red cells sensitized with anti-Rh could be inhibited by adding human gamma-globulin to the antiglobulin serum, and they concluded that incomplete anti-Rh must consist predominantly of gamma-globulin. For several years it was thought that anti-gamma-globulin was the only important constituent in antiglobulin serum. Then Dacie (1951) found that an antiglobulin serum to which gamma-globulin had been added would still react with the red cells of patients with the "cold antibody" type of haemolytic anaemia, and others found that anti-globulin sera which had been absorbed with red cells sensitized with one kind of antibody might still react with red cells sensitized with other kinds of antibody (Crawford and Mollison, 1951; Renton, 1952).

It was found that an antiglobulin serum completely lacking anti-gamma-globulin might react with red cells sensitized with certain antibodies (for example, anti-Le^a), and it was concluded that some antibodies consist of "non-gamma"-globulin—that is, beta- or alpha-globulin (Cutbush, Crawford, and Mollison, 1955). Some antibodies of this kind were found to be detectable in the antiglobulin test only when fresh serum was used to sensitize the cells (Mollison and Cutbush, 1955). It was then demonstrated that in certain cases the antiglobulin serum was reacting with complement adsorbed on to the sensitized cells rather than with the antibody itself (Dacie, Crookston, and Christenson, 1957). It was now realized that, at least in most cases, the antibody itself was a gamma-globulin and the "non-gamma"-globulin was complement.

The binding of complement to red cells sensitized with antibody can be demonstrated in other ways—namely, either by showing that under suitable conditions haemolysis occurs or by the use of a serum containing conglutinin (Streng, 1930).

A few human blood-group antibodies will haemolyse untreated red cells in the presence of human complement—namely, many examples of anti-A and anti-B, anti-Le^a, and perhaps all examples of anti-P + P_1 (anti-Tj^a). Other antibodies will lyse enzyme-treated cells: probably all examples of anti-A, anti-B, and anti-Le^a, many examples of anti-Le^b and anti-Jk^a, and some examples of anti-P_1. If rabbit serum rather than human serum is used as a source of complement all these antibodies and several others (some examples of anti-S, anti-K, and anti-Fy^a) will haemolyse untreated red cells (Mollison and Thomas, 1959).

The binding of human complement (or animal complement) to red cells sensitized with all the complement-binding antibodies referred to in the preceding paragraph can also be demonstrated by testing the cells with a rabbit serum containing immuno-conglutinin (Mollison and Polley, 1959).

Some of these reactions are summarized in Table IV. Red cells sensitized with anti-Le^a in the presence of complement are not agglutinated by an anti-gamma-globulin serum, but they are agglutinated by an anti-"non-gamma"-globulin serum. Similarly, they are agglutinated by a serum containing immuno-conglutinin. Sera containing anti-Le^a and complement will often lyse untreated red cells. More rapid and complete lysis is observed if rabbit complement is added or if the cells are first treated with an enzyme.

TABLE IV.—*Tests for Complement-binding by Human Blood-group Antibodies*

Red Cells Incubated with Antibody*	Agglutination by Anti-human Globulin Sera		Agglutination by Rabbit Immuno-conglutinin Serum	Haemolysis with	
	Anti-gamma-globulin	Anti-"non-gamma"-globulin		Human Complement	Rabbit Complement
Anti-Le^a ..	−	++	++	±	++
Anti-Fy^a (some†)	+	++	++	−	++
Anti-Rh ..	+++	−	−	−	−

* And human complement.
† Only some examples of anti-Fy^a bind complement.

Red cells sensitized with some examples of the anti-Fy^a behave similarly, the only differences being that some reaction is obtained between sensitized red cells and an anti-gamma-globulin serum and that no reaction is obtained with enzyme-treated cells (since the Fy^a antigen is destroyed by the enzyme).

Red cells sensitized with incomplete anti-Rh are strongly agglutinated by anti-gamma-globulin, but they give none of the reactions which would be expected if complement were bound.

This difference between the behaviour of antibodies *in vitro*—some binding complement and some failing to bind complement—is reflected in differences in the way in which the same antibodies bring about the destruction of red cells *in vivo*, as is discussed later.

Survival of Transfused Red Cells

One criterion of a successful red-cell transfusion is that the survival of the red cells should be maximal—that is, not curtailed by serological incompatibility. The first quantitative estimates of red-cell survival following transfusion were made by Todd and White (1911) in cattle. By absorption, they prepared a serum which would lyse the red cells of one animal but not those of another. After cross-transfusion between the two animals they analysed samples of blood and determined the percentage of transfused red cells at different intervals after transfusion. They found that the number of surviving cells fell progressively, and reached zero after four or five days. On the fifth day a haemolysin active against the donor's red cells was first detected, and this increased in titre to reach a peak about ten days after transfusion. Todd and White concluded: "The implications for human blood transfusion are obvious," but fortunately this interpretation was wrong.

In 1919, Winifred Ashby, working at the Mayo Clinic, applied differential agglutination (rather than differential lysis) to the investigation of red-cell survival in man. After transfusing group O blood to group A recipients she took samples and incubated them with anti-A. It was thus possible to make estimates of the survival of the group O (unagglutinated) cells.

For 20 years or so little use was made of Ashby's method, perhaps mainly because, owing to incomplete agglutination of A cells, it was difficult to obtain quantitative estimates. At the beginning of the second world war the method was used to estimate the survival of red cells after storage, and this called attention to its value. Then followed the era of application of the method to the investigation of haemolytic anaemias, which yielded a spate of information and altered ideas of the classification of this large group of diseases.

Application of the method of differential agglutination to the investigation of blood-group incompatibility began with the studies of Wiener (1941). These studies were essentially qualitative. Thus in most cases Wiener made use of differences between donor and recipient with regard to MN type and simply tested for the presence or absence of cells of the donor's type. Others made attempts to obtain quantitative information, but this could be done only when the antibody was very weak, since relatively large volumes of incompatible red cells had to be detected to obtain useful results. Even when 50 ml. of blood was transfused to an adult, only very crude quantitative data could be obtained (see Mollison, 1951, p. 301).

The availability of radioactive isotopes in the past decade has altered the position. Not only can relatively minute volumes of red cells (less than 1 ml.) be labelled, but results of great precision can be obtained. Two convenient labels are available: ^{51}Cr and ^{32}P. ^{51}Cr is the more useful, since the rate of "elution" from labelled red cells in the circulation is relatively slow. Thus, about 3% leaks out in the first three to five hours and 5–6% in the first 24 hours; thereafter the rate of loss is much slower. By contrast about 10% of ^{32}P leaves the red cells in the first hour after injection, and more than 50% in the first 24 hours. ^{32}P can thus be used as a label for incompatible cells only when the investigation is to be limited to a period of about 60 minutes after injection. However, ^{32}P is very suitable as a label for compatible cells to be injected as a control; the cells are best obtained from the subject in whom the test is to be made. Thus, in a typical test, 2–3 ml. of the subject's own red cells are labelled with ^{32}P (as phosphate), and 0.1–1 ml. of the donor's red cells are labelled with ^{51}Cr (as chromate). After labelling, the red cells are mixed and injected as a single suspension.

Validity of Results Obtained with Very Small Transfusions

The advantage of using 1 ml. or less of red cells for a test of compatibility is mainly that the development of symptoms of any kind is unlikely. The potential disadvantage is that the pattern of destruction of 1 ml. of red cells may differ considerably from that of 500 ml. or 1,000 ml.

The destruction of a relatively large volume of red cells may be limited in two ways. Firstly, if a sufficient volume of blood is transfused, all the circulating antibody (and/or complement) may be adsorbed on to the transfused red cells, and red-cell destruction may then be virtually arrested until the recipient produces more antibody. An example of this is given in Fig. 1.

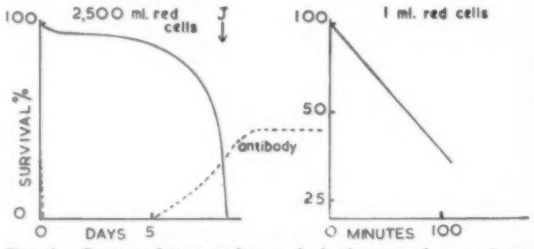

FIG. 1.—Contrast between the survival of a very large volume and a very small volume of incompatible red cells. After the transfusion of 2,500 ml. of red cells, all antibody (anti-Fy^a) disappeared from the circulation for about five days, and during this period there was no destruction of incompatible red cells. Then antibody reappeared, the incompatible red cells were rapidly destroyed, and the patient became jaundiced (J). When a test was made later with only 1 ml. of red cells the cells were cleared from the circulation with a half-time of about 70 minutes.

(The limitation of red-cell destruction by exhaustion of antibody was demonstrated in dogs by Christian *et al.* (1951).)

In man the transfusion of 500–1,000 ml. of incompatible blood will absorb all circulating antibody only when the antibody is very weak. For example, in one case in which the patient's serum contained Rh antibody with a titre of only 2, and 500 ml. of Rh-positive blood was transfused, antibody could not be demonstrated in the serum during the following 48 hours (Mollison and Cutbush, 1955, Case 7). In a patient whose serum contained an anti-B agglutinin with a titre of 32 the transfusion of 1,000 ml. of blood led to the disappearance of antibody from the circulation for about five days. Probably, incomplete antibodies are less easily absorbed than agglutinins. Thus, in a patient whose serum contained anti-c with a titre of 8, the transfusion of 500 ml. of incompatible blood failed to remove all free antibody, and the incompatible red cells underwent steady destruction after transfusion (see Fig. 2).

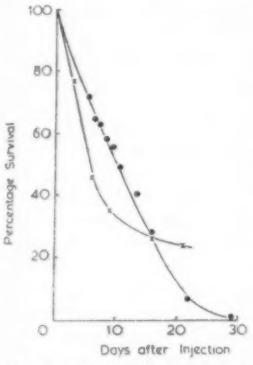

FIG. 2.—Contrast between the survival of a moderately large volume and a very small volume of incompatible red cells. After the transfusion of approximately 200 ml. of red cells the titre of antibody (anti-c) fell slightly; red-cell destruction, though slow, was continuous (●——●). Presumably the rate of red-cell removal was not limited by the capacity of the reticulo-endothelial system in this case. Five weeks later, when 1 ml. of red cells was injected, the rate of destruction was only slightly more rapid (×——×). (Redrawn from the data of Mollison and Cutbush, 1955.)

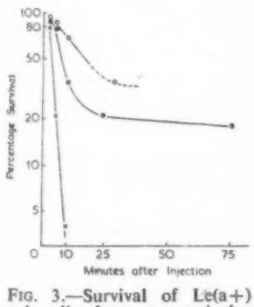

FIG. 3.—Survival of Le(a+) red cells from a particular donor (H. L.) after injection into three recipients whose serum contained anti-Le^a; in each case the titre of the serum was estimated by the indirect antiglobulin technique. ×——×=titre 32; ●——●=titre 8; O——O=titre 1. (From Mollison and Cutbush, 1955.)

When the patient's serum contains a potent antibody the transfusion of even 2,000 ml. of blood may fail to absorb all circulating antibody (see a case described by Mollison, 1956, as Case A in Fig. 2 on page 347, in which 2,000 ml. of Rh-positive blood was transfused to a patient whose serum contained potent incomplete Rh antibody).

The rate of destruction of amounts of incompatible blood which are too small to absorb all circulating antibody, or even to reduce its titre, may be limited by the capacity of the reticulo-endothelial system. Thus, according to Dr. C. A. Finch (personal communication) the reticulo-endothelial system can remove from the circulation only about 30 ml. of red cells per hour. Therefore, for example, after the transfusion of 2,000 ml. of Rh-positive blood (equal very approximately to 1,000 ml. of red cells) the elimination of red cells from the circulation would be expected to take more than 24 hours; this is in fact what has been observed (see Case A referred to in the preceding paragraph).

When the antibody concerned is capable only of slow red-cell destruction, so that the capacity of the reticulo-endothelial system to take up cells is not exceeded, small amounts of red cells may not be removed any more rapidly than large amounts. Fig. 2 shows a case in which a patient whose serum contained anti-c (titre 8) received a transfusion of 500 ml. of c-positive blood. After the red cells had been eliminated (at a very slow but steady rate) an injection of 1 ml. of c-positive red cells was given. The red cells were eliminated only slightly more rapidly than on the first occasion. This suggests that the slower elimination of the larger amount was due solely to the slight lowering of the titre of anti-c, and was not due to overloading of the capacity of the R.-E. system.

It might be thought that when only 1 ml. of incompatible cells was injected even a very weak antibody would be able to bring about their immediate destruction; but this is not the case. Thus, Fig. 3 shows the survival of Le(a+) cells in three recipients whose serum contained varying amounts of anti-Le^a. In the first, who was a patient who had developed haemoglobinuria after the transfusion of a bottle of Le(a+) blood and whose serum had an indirect antiglobulin titre of about 32, practically all the injected red cells were removed with a half-time of about two minutes.

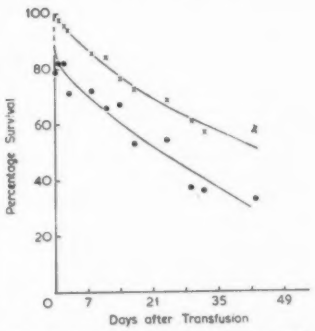

FIG. 4.—Survival of A$_1$, Le(a−b−) red cells (×——×), estimated by ^{51}Cr-labelling and corrected for Cr elution, and of O, Le(a−b+) red cells (●——●) estimated by differential agglutination, in the circulation of a patient whose serum contained anti-Le^a. (From Cutbush *et al.*, 1956.)

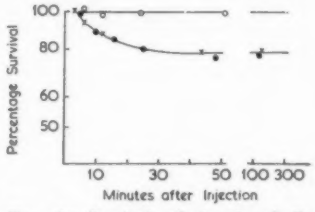

FIG. 5.—Survival of 1 ml. of O, Le(a−b+) red cells on two separate occasions (●——● and ×——×) after injection into the patient referred to in Fig. 4. The donor was one of two who gave blood for the transfusion illustrated in Fig. 4. O——O=Survival of red cells from a group A$_1$, Le(a−b+) donor. (From Cutbush *et al.*, 1956.)

In the second recipient, who was a patient who had developed jaundice after a bottle of Le(a+) blood and whose serum had an indirect antiglobulin titre of about 8, approximately 80% of the cells were removed with a half-time of three minutes. In the third, who was a normal subject whose serum reacted only very weakly at 37° C. (titre 1), 65% of the red cells were removed with a half-time of six minutes and the remainder were removed very much more slowly.

A further example of the similarity of results observed with small and large volumes of incompatible red cells is provided by Figs. 4 and 5. A patient whose serum contained anti-Le^a was transfused with 500 ml. of group O, Le (a−b+) blood (250 ml. from each of two donors). The number of red cells transfused was very carefully

estimated, as was the concentration of transfused cells in the recipient's circulation after transfusion. The red cells were transfused in 80 minutes; a sample was taken a few minutes later. This sample contained only 80% of the expected number of transfused cells, as Fig. 4 shows. Later, several tests were made using only 1 ml. of group O, Le(a – b +) red cells, including red cells from one of the two donors previously used. As Fig. 5 shows, 20% of the injected red cells were removed during the 20 minutes following injection, the remaining cells surviving for a much longer period.

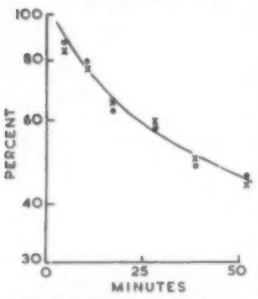

FIG. 6.—Estimates of haemoglobin (×) and ^{51}Cr (●) in the plasma after the injection of ^{51}Cr-labelled haemoglobin into a rabbit. The estimates are shown as percentages of values predicted from the amount of haemoglobin injected and the known plasma volume.

It may be concluded that a test using 1 ml. of incompatible red cells gives reliable information about the proportion of red cells which will be destroyed, although the rate of destruction of the large volume will usually be slower.

^{51}Cr as a Label for Haemoglobin.—When ^{51}Cr-labelled sodium chromate ($Na_2{}^{51}CrO_4$) is added to red cells, chromate rapidly passes into the red cells and is then apparently reduced to the trivalent cationic form and labels haemoglobin (Gray and Sterling, 1950). If the red cells are now haemolysed, and the haemoglobin is separated from the stroma, virtually all the radioactivity is found to be associated with the haemoglobin. If this haemoglobin is injected into the circulation, the ratio of haemoglobin to radioactivity remains constant for a period of approximately one hour after injection (see FIG. 6). Thereafter haemoglobin is cleared from the circulation more rapidly than ^{51}Cr, evidently because ^{51}Cr exchanges between haemoglobin and plasma proteins (Jandl *et al.*, 1957). Thus over a period not exceeding one hour ^{51}Cr is a useful label for haemoglobin in the plasma.

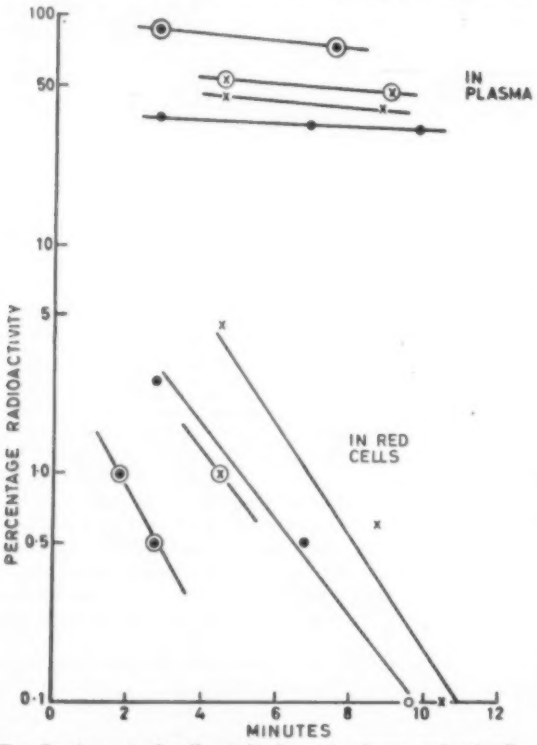

FIG. 7.—Amount of radioactivity found in plasma and red cells after injecting approximately 0.5 ml. of ^{51}Cr-labelled red cells of incompatible ABO group into two human subjects (●——●=A_2 cells injected into a group O recipient; ⊙=B cells injected into a group A recipient) and after injecting human group O red cells into two rabbits (× and ⊛).

Intravascular Lysis

Fairley (1941) suggested that there were two major modes of red-cell destruction: intravascular and extravascular. Studies with ^{51}Cr confirm this, although they show that in cases in which lysis is predominantly intravascular some red cells are usually removed intact from the circulation and that in destruction which is predominantly extravascular some haemoglobin is liberated into the plasma. Intravascular haemolysis of incompatible red cells is seen characteristically when antibodies which are readily haemolytic *in vitro* are involved. Thus Fig. 7 shows two examples of the removal of human red cells from the circulation of humans by haemolytic anti-A and anti-B, and also shows two examples of the removal of human red cells from the circulation of a rabbit by haemolytic anti-human red-cell antibody. In each of the four cases more than 90% of the cells were removed from the circulation within five minutes of injection and 40–90% of the injected radioactivity was found in the plasma.

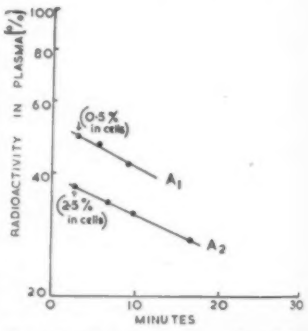

FIG. 8.—Amount of radioactivity found in plasma and red cells after injecting approximately 0.5 ml. of cells of subgroups A_1 and A_2 respectively into a group O recipient.

In this type of destruction the weaker the haemolysis *in vitro* the smaller is the percentage of cells destroyed intravascularly. Fig. 8 shows the results in a group O subject infected with A_1 and A_2 cells on different occasions. *In vitro*, the A_2 cells were lysed to a lesser extent than the A_1 cells, and *in vivo* the proportion of haemoglobin appearing in the plasma after the injection of A_2 cells was less—that is, more cells were removed intact from the circulation.

Extravascular Destruction

Practically all human blood-group antibodies other than some examples of anti-A and anti-B are not readily lytic *in vitro*, and they bring about predominantly extravascular destruction. Fig. 9 shows, for example, the rate of clearance of Rh-positive red cells sensitized with Rh antibody. The cells are cleared from the circulation with a half-time of approximately 20 minutes, indicating removal predominantly in the spleen (Mollison and Cutbush, 1955; Hughes Jones *et al.*, 1957), and the maximal level of radioactivity in the

plasma (indicating approximately the level of free haemoglobin in the plasma: see above) reached about 3% of the total amount of haemoglobin injected in the form of intact red cells (Fig. 9).

Apparently the proportion of haemoglobin liberated into the plasma depends upon the amount of red cells injected. Thus, Jandl *et al.* (1957) found that when

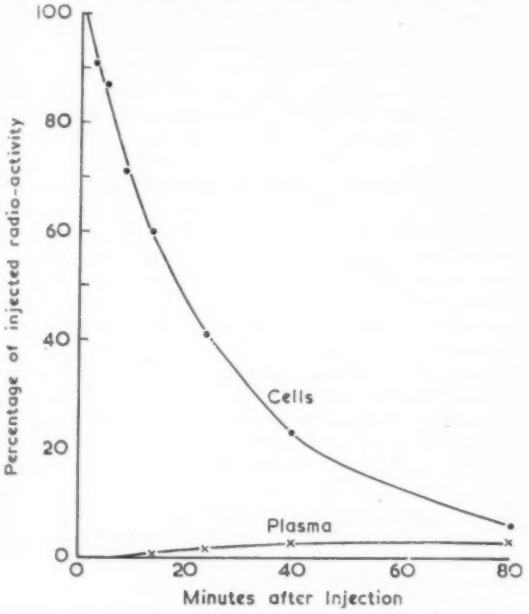

FIG. 9.—An example of predominantly extravascular destruction. 0.4 ml. of Rh-positive red cells was labelled with ^{51}Cr, then sensitized *in vitro* with Rh antibody and reinjected into the donor. The red cells were removed from the circulation with a half-time of approximately 20 minutes; the amount of radioactivity in the plasma never exceeded 3% of the total amount injected in the form of labelled red cells.

amounts of Rh-positive red cells equivalent to 3 g. of haemoglobin were injected into subjects whose serum contained anti-Rh the maximal level of plasma haemoglobin was usually equivalent to about 5% of the total dose injected, but when the amount of red cells was equivalent to about 7 g.—that is, about 50 ml. of blood—the maximal plasma haemoglobin level was equivalent to about 10% of the injected dose. Presumably when larger doses, of the order of 500 ml. of incompatible blood, are transfused an even higher proportion of the haemoglobin from destroyed red cells is likely to spill into the circulation, since haemoglobinuria does occasionally occur after haemolytic transfusion reactions due to anti-Rh (Vogel *et al.*, 1943).

When destruction is predominantly extravascular, the localization of the ^{51}Cr-labelled cells can be determined by surface counting—that is, counting over the surface of the body with a scintillation counter.

Surface Counting.—The gamma rays emitted by ^{51}Cr are very readily absorbed by tissues, and thus, owing to differences in bodily configuration, it is not possible to make precise quantitative estimates of the distribution of ^{51}Cr in different organs. However, it is possible to make rough quantitative estimates, and it is often possible to conclude that the greater part of the activity is localized in some particular organ—for example, the spleen. Interpretation of the findings is made easier by calibrating the particular scintillation counter used with models of the liver and spleen containing known amounts of radioactive chromium. Thus, Mollison and Hughes Jones (1958) made models out of agar, incorporating known amounts of ^{51}Cr, placed the models in a dead body, and then carried out surface counting. They found that when the liver and spleen were of a normal size a given amount of radioactivity in the spleen gave a counting rate which was three times higher than that for the same amount of radioactivity in the liver. By counting different models in different bodies they arrived at average figures expressed as counts per second per microcurie for ^{51}Cr in the normal liver and normal spleen, and they used these figures to make estimates of the amount of red cells trapped in the liver and spleen after injecting incompatible red cells. These estimates are referred to below.

Summary of the Capabilities of ^{51}Cr

Radioactive chromium is thus an extremely useful label for incompatible red cells. Volumes of less than 1 ml. can be easily and rapidly labelled *in vitro*. If the red cells are destroyed intravascularly the amount of haemoglobin set free in the plasma can be estimated. If they are destroyed extravascularly their main sites of destruction can be identified, and an approximate estimate made of the proportion of red cells destroyed there. Finally, ^{51}Cr can easily be counted in the presence of ^{32}P, which can be used to label a control sample of compatible red cells. This makes it possible to detect the destruction of even 5% of incompatible red cells.

With such a test system the effects of different antibodies on the destruction of injected red cells can be accurately determined.

[*The second lecture, with a list of references, will appear in our next issue.*]

MAXIMUM FORCED EXPIRATORY FLOW RATE AS A MEASURE OF VENTILATORY CAPACITY

WITH A DESCRIPTION OF A NEW PORTABLE INSTRUMENT FOR MEASURING IT

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The use of a single forced expiration as a method of assessing ventilatory capacity is becoming increasingly popular, mainly because, as pointed out by Kennedy (1953), it is a much simpler and less tiring procedure than the maximum voluntary ventilation (M.V.V.).

The basis of most of the various single-breath methods is the same: the volume of air expired is measured against time by means of a spirometer with either a recording drum or a timing device. There are some differences of opinion about the most suitable interval of time over which to measure the volume and about the relative merits of a recording drum or a timing device, but it is generally agreed that methods of this kind are clinically valuable and give results which are comparable

with those of the M.V.V. All the methods, however, suffer from the disadvantage that the necessary apparatus is cumbersome and normally requires connexion to an electric supply. Attention has therefore been directed to the possibility of using the maximum forced expiratory flow rate (or "peak flow rate"), instead of what is in effect the average for a limited time, as a measure of ventilatory capacity; such a measurement seemed likely to lend itself to the use of a simpler instrument, consisting merely of a flowmeter with a device for recording the maximum.

According to Donald (1953) the empirical use of a measurement of this kind is very old. "The physician of the last century who asked a patient with respiratory disease to whistle or blow a candle out was crudely assessing the maximum respiratory velocities" (*sic*). Donald suggested that a "simple, whistle-like instrument" might be developed and might become a standard clinical tool.

In this paper an instrument of this kind is described, but first it may be useful to give an account of the maximum forced expiratory flow rate as a physiological measurement.

Historical

Apart from the rather vague reference quoted by Donald the earliest systematic attempt to use the peak flow rate as a physiological index was that of Hadorn (1942), who measured the flow rate on expiration by means of an aneroid manometer connected across a simple orifice. The resistance of the system was high, as much as 32 cm. of water at a flow of 500 l./min., and no provision was made for recording the maximum deflection of the manometer pointer except judging it by eye. The highest flow rates he recorded were about 500 l./min. Wyss (1950) used the same type of orifice as Hadorn, but recorded the pressures photographically, using a membrane manometer and an optical lever. This gave a permanent record and a higher frequency response. He registered flow rates as high as 720 l./min.

The basic method used by both these workers has the disadvantage that the pressure drop across a simple orifice varies as the square of the flow rate, with the result that the higher flows are considerably reduced, thus cramping the scale of the measurement. In addition the sensitivity of the method at low flow rates is low, giving an unsatisfactory logarithmic scale. Nevertheless, an instrument of this kind has been produced commercially and has been the basis of a number of studies of the relationship between the maximum forced expiratory flow rate and the vital capacity (Hildebrandt and Hanke, 1956). The instrument, called a "pneumometer," incorporates an aneroid manometer fitted with a device for recording the maximum flow rate. Rates up to about 700 l./min. can be recorded.

Of recent years the use of improved forms of pneumotachograph (Silverman and Whittenberger, 1950; Lilly, 1950) has led to many observations of the expiratory flow pattern, but no systematic attempt to use the peak flow rate as a physiological measurement in its own right appears to have been made. Moreover, although the pneumotachographs themselves have had very low resistances (of the order of 2 mm. H_2O/100 l./min.) which gave a linear relationship between flow and pressure, for some reason which is not clear they seem to have sometimes produced a considerable reduction in peak flow rate in healthy normal men. For instance, Shephard (1955), measuring peak flow rates during a forced expiration in "healthy young adults," recorded none higher than 427 l./min., and one of only 183 l./min. in an apparently healthy man of 25. Similarly, Leuallen and Fowler (1955) found no flows higher than 660 l./min. in a group of normal males; and Comroe, Forster, Dubois, Briscoe, and Carlsen (1955) quote 500 l./min. as a "typical figure" for a "maximum expiratory flow rate." In their table of "normal values," however, they quote a figure of 400 l./min. and make it clear that this is averaged over a volume of one litre. In contrast, as will be seen, we have found that peak flow rates over 700 l./min. are common in adult males and flows up to nearly 1,000 l./min. by no means rare. To measure such flows it has been necessary to make use of an enlarged version of the Lilly pneumotachograph with connexions of very wide bore. Details of this instrument are given later.

For two reasons it is desirable to measure the peak flow rate in such a way as to get the maximum possible figure. In the first place, the higher the figures given by normals the more clearly they are differentiated from the abnormals, whose relatively low flow rates are less affected by resistance, especially if it is non-linear in type. Secondly, one important advantage of the peak flow rate as a physiological index is that it is relatively easily understood and defined. Respiratory physiology is beset with measurements which are peculiar to the instrument and the laboratory where it is made (Comroe *et al.*, 1955), and therefore it is highly desirable that, if possible, a measurement should be absolute, and clearly defined, so that it will be the same however and wherever it is measured.

Both the earlier and the latest forms of pneumotachograph suffer from the disadvantage of being fairly complicated and not easily portable. A much simpler and more robust and portable instrument, designed specifically for measuring the peak flow rate, has been described by Goldsmith and Young (1956) and called by them the "puffmeter." It is of basically the same design as the Lilly and Silverman pneumotachographs, but uses a robust ceramic grinding wheel as a linear resistance and an aneroid manometer to measure pressure.

It appears to suffer from two disadvantages; the pressure drop across the resistance is relatively high, about 1 cm. H_2O/100 l./min., and the maximum reading has to be read off from a presumably rapidly moving hand on a dial. Nevertheless, Goldsmith (1958) has used it extensively, and by calibrating it empirically against a pneumotachograph he has obtained a considerable body of data about peak flow rates. Unfortunately, his results are all given in "puffmeter" units, which are admitted to be much lower than the actual flow measured with a pneumotachograph. He calibrated the puffmeter by connecting it to the outlet of a Lilly pneumotachograph, using peak flows varying from 100 to 700 l./min. produced voluntarily by one individual; from this he claimed to be able to estimate the true figures. His mean values for a "normal reference population" aged 40–65 and free of all apparent respiratory disability, translated into absolute units in this way, were about 600 l./min. for men and 450 l./min. for women. These results are difficult to compare with our own because of the very wide age group for which they are given, but they appear to be compatible with them.

Before we became aware of the pneumometer or of Goldsmith's work with the puffmeter, a quite different

type of instrument was developed for the same purpose. It seems to have some advantages over the pneumometer and the puffmeter in that it is simpler and more easily portable, and has a lower resistance at high flow rates.

The Peak Flow Meter (P.F.M.)

This instrument operates on different principles from any used hitherto for this purpose, being of the class of flowmeter known as a "variable area orifice meter," of which the best-known example is the rotameter (see Linford, 1949).

This type of meter has a number of advantages for respiratory measurements. It can make use of the fact that, although only a small resistance can be tolerated, an expiration has large volume, so that a very simple and robust instrument can measure rapidly changing flows with quite sufficient accuracy. Although the pressure drop at low flow rates is higher than that of plain orifice-type instruments it rises only ten times over the whole range from 100 to 1,000 l./min., so that at high flow rates the resistance is comparable to that of Goldsmith's puffmeter.

The principle of operation of the instrument is illustrated diagrammatically in Fig. 1. A cylindrical cavity about 5 in. (12.7 cm.) in diameter and 1½ in. (3.6 cm.) deep has a radial inlet nozzle (1), and contains a movable vane (2) pivoted in the centre of the cylinder and fitted closely without touching. A fixed partition (3) extends from one side of the inlet orifice to within a short distance of the boss of the vane, but again does not touch it. A spiral spring (4) attached to one end of the spindle of the vane tends to rotate it towards the

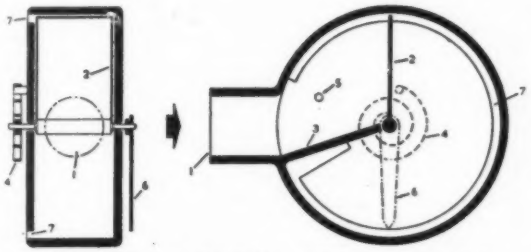

FIG. 1.—Diagram of peak flow meter. For key see text.

inlet orifice, a stop (5) preventing it from passing the orifice. A pointer (6) on the other end of the spindle indicates the position of the vane on a dial (not shown) and also serves to counterbalance it. An annular orifice (7) extends round the periphery of the cylinder at the back, from one side of the inlet orifice to the other.

It can be seen that when air is blown into the instrument it cannot escape (except for a small amount which leaks past the vane) until the vane has moved and uncovered part of the annular orifice. When the area of orifice uncovered is such that the pressure behind the vane is just sufficient to balance the force of the spring, the vane will come to rest in a position which will depend on the flow rate. Since for a given pressure the rate of flow is proportional to the area of the orifice, the deflection of the vane would be proportional to the air flow if the tension of the spring were constant. In practice, the tension of the spring increases with the deflection, so that the deflection is proportionately less at high flows than at low. This has the effect of increasing the range of the instrument without loss of sensitivity at the lower end of the range, so that flows from 50 to 1,000 l./min. can be covered in one instrument.

The instrument is fitted with a ratchet which holds the vane and pointer in the position of maximum deflection. They can be returned to zero by pressing a release button.

The general appearance of the instrument, which weighs about 2 lb. (900 g.), and its method of use are shown in Fig. 2. The subject is asked to take a deep breath, as for a vital capacity, to place the mouthpiece in his mouth, and then to blow into the instrument as hard as he can. It is not necessary to try to empty the lungs, and it is undesirable to do so, because it is unpleasant and tiring, but a certain amount of "follow through" is required. After a couple of practice blows, three attempts in succession are recorded and the average is taken. This is statistically a more satisfactory procedure than simply taking the highest reading, although logically the latter would be preferable, since a maximum is being measured. Most subjects will give three readings which agree within 10% after the practice tries, but the observer must ensure that the subject is really trying his hardest. As with all ventilatory tests of this kind, including the M.V.V., failure to produce reasonably concordant readings usually indicates lack of co-operation.

FIG. 2.—Peak flow meter, showing method of use.

The instrument is supplied with a plastic mouthpiece, which can be easily removed for washing and sterilization. Disposable cardboard mouthpieces are also available. A removable coarse-mesh gauze in the inlet nozzle prevents the ingress of large particles of sputum, etc.

Performance Tests

The P.F.M. was originally developed as a largely empirical device, and it has only recently been possible to arrange for satisfactory physical and physiological testing. Two forms of calibration have been used—with steady and with transient flows.

Steady-flow Calibration

Because of its low resistance the instrument can be easily calibrated by simply blowing air through it in series with a rotameter. Calibration in this way of an instrument with a dial graduated in degrees gives a curve of the form shown in Fig. 3. The curve does not pass through the origin, because even when the annular orifice is completely shut off there is some leakage round the vane; a certain minimum flow is therefore needed to deflect the vane against the spring. The exact

calibration of the instrument in this range is thus liable to be much affected by the accuracy of construction, so that steady-flow calibration is a convenient method of checking this point. Fig. 3 also shows the relationship between flow rate and pressure

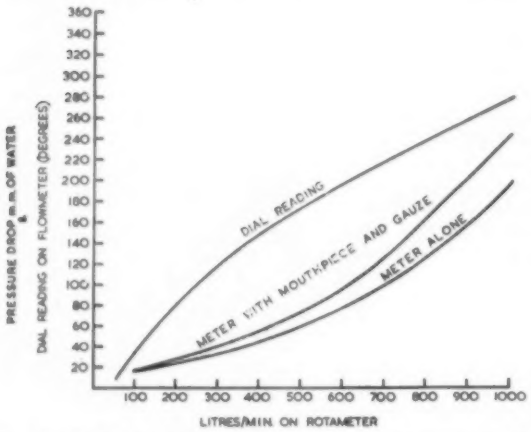

FIG. 3.—Steady flow calibration curve of peak flow meter and pressure/flow curves with and without inlet gauze and mouthpiece.

drop through the instrument. At low flow rates the pressure drop is relatively high, but it rises only slowly with increasing flow rate. At high flow rates the fixed orifice component of the resistance comes more and more into play and the pressure drop increases more steeply. The additional resistance of the mouthpiece and gauze, of which the latter is the main component, is also more important at higher flow rates; this additional resistance has been found to be an advantage in practice, as it makes the instrument more comfortable to blow into, and it does not appreciably affect even high peak flows.

Transient-flow Calibration

The only instrument which can be used to test the ability of the P.F.M. to measure very transient flows is a pneumotachograph. As already noted, the one we have used is an enlarged version of that described by Lilly (*loc. cit.*), and gives an approximately linear response to flows up to 1,000 l./min. It has a resistance of 400-mesh gauze, 4 in. (10.2 cm.) in diameter, giving a pressure drop of 1 mm. H_2O/100 l./min. The entry and exit cones connect to tubes 1¼ in. (3.2 cm.) internal diameter, and the subject blows through a mouthpiece connected to the instrument by 10 in. (25.4 cm.) of hose of 1½ in. (3.8 cm.) internal diameter. The overall pressure drop through the complete instrument, including the mouthpiece, is 1.5 cm. H_2O at 700 l./min.

A capacitance manometer is used to convert the pressure into an electric signal, which is suitably amplified and recorded by a "mingograf" spray writing pen. This instrument has a high-frequency response which sometimes makes its records difficult to interpret owing to the amount of "noise" recorded. It is therefore used with a 1 μF condenser connected across its input.

For technical reasons it is not convenient to connect the P.F.M. in series with the pneumotachograph. It has also proved impossible so far to produce artificial peak flows of sufficiently smooth wave form for satisfactory recording by the pneumotachograph. The procedure, therefore, has been to ask a series of subjects to blow alternately into the P.F.M. and the pneumotachograph. Usually three blows into each instrument are used and the instrument to be blown into first is alternated between subjects.

Although this procedure is rather laborious and time-consuming it has the two great advantages that the calibration is carried out on actual human peak flows, and that the question of whether the resistance of the P.F.M. modifies the peak flow does not arise. On the other hand, the scatter of readings is increased because the two instruments are in fact measuring different peak flows; this scatter can be reduced by taking a large number of readings and averaging them, but with any practicable design of experiment the scatter from this cause is inevitably considerable.

Another difficulty that arises when an attempt is made to use pneumotachograph recordings to measure the peak flow rate is the practical definition of the term "maximum expiratory flow rate." Fig. 4 shows a drawing of a pneumotachograph recording of a typical normal forced expiration. It will be seen that in this case the definition and measurement of the maximum expiratory flow rate present no difficulty. Fig. 5, on the other hand, shows a type of record that is sometimes obtained from abnormal subjects, where the maximum

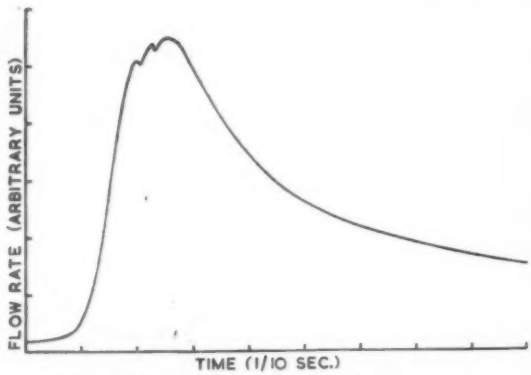

FIG. 4.—Normal type of forced expiratory curve.

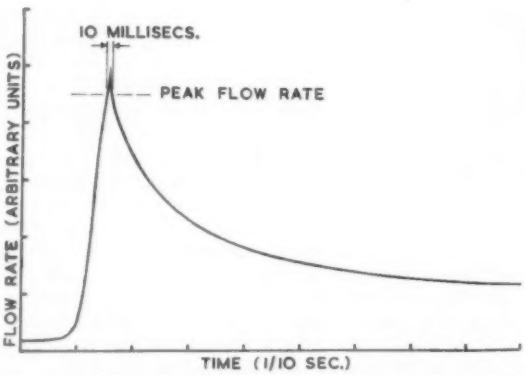

FIG. 5.—Abnormal type of forced expiratory curve, showing method of deciding level of peak.

is in the form of a sharp "peak" which is sustained for only a very short time.

To take the top of a peak of this kind as the maximum is unsatisfactory for two reasons. First, the actual height of the peak is critically dependent on the characteristics of the recording instrument. Secondly, the volume of air represented by quite a large change in peak level is very small, so that it is likely to have little physiological significance. On both instrumental and physiological grounds, therefore, it has seemed to us better to ignore the top of the peak and to take a level of flow which is sustained for a definite time as being what we call the "peak flow rate" (P.F.R.). An interval of 10 millisecs was chosen as being the shortest which lent itself to reasonably accurate measurement of the peak on a pneumotachograph record. The P.F.R. is therefore defined as the highest flow rate sustained for at least 10 millisecs (cf. McKerrow *et al.*, 1958).

As can be seen from Fig. 5, although this definition is fairly easy to understand, the actual measurement of peak levels defined in this way sometimes presented some difficulty, owing to the steepness of the sides of the peak, even when recorded on paper moving as fast as 10 cm./sec. There was thus room for considerable observer error in making the measurement, but by averaging the results of a number of recordings fairly stable figures could be obtained.

A number of calibrations of different models of P.F.M.s were carried out in the way described, using a variety of subjects ranging from children of 4 years to healthy male adults capable of peak flows up to nearly 1,000 l./min. and also including many seriously disabled patients. It soon became apparent that, although the P.F.M. tended to underestimate the P.F.R. as recorded by the pneumotachograph, the relationship between its reading and that of the pneumotachograph was remarkably consistent.

The reason for the underreading of the P.F.M. is rather obscure. It is probably due chiefly to the fact that the instrument is highly damped and therefore fails to reach equilibrium in the short time available.

In view, however, of the high correlation obtainable between the P.F.M. and the pneumotachograph it seemed legitimate to aim at producing an instrument with a dial graduated in litres/min. peak expiratory flow rate. This would conceal to some extent the fact that the relationship between the P.F.R. recorded by the P.F.M. and that recorded by the pneumotachograph was not perfectly constant, and in particular the fact that it was liable to vary at different levels of flow and with different patterns of expiration, but such a loss of information seemed amply compensated by the simplification in the use of the instrument that would result. To have an instrument with a dial calibrated in degrees, or in "peak flow units," and supply various calibration curves to the user did not seem reasonable in view of the relatively small differences involved, especially for an instrument intended primarily for clinical use.

When carrying out the final calibration of the prototype production instrument, therefore, the procedure was as follows: A group of 20 normal subjects (male and female, ranging in age from 15 to 69), 10 children (male and female, ranging in age from 5 to 11), and 20 male patients (mostly suffering from pneumoconiosis, ranging in age from 30 to 70) was used. A much larger and more heterogeneous group would obviously have been desirable, but the time and labour available for carrying out the calibration were unfortunately limited. Each subject made two practice blows, and then three blows into the P.F.M. and the pneumotachograph alternately, the order of starting being reversed after each subject. The calibration of the pneumotachograph was checked against a rotameter after each subject, and also by integrating some of the curves and comparing them with the forced expiratory volume (F.E.V.) recorded with a Gaensler (1951) type of apparatus. The overall accuracy of the instrument was considered to be $\pm 5\%$.

The steady-flow calibration of the P.F.M. was also checked at intervals, and was found to be constant within the limits of accuracy with which it could be determined—that is, about $\pm 2\%$.

Fig. 6 shows the result of the P.F.M./pneumotachograph calibration. The P.F.M. results are recorded in degrees, and each point is the average of the three readings. It can be seen that there is considerable scatter in the results, which for the reasons given above is inevitable, but a simple curve cutting the abscissa at 50 l./min., the point at which the P.F.M. ceases to record, can be quite easily fitted. The equation of this curve, for which we are indebted to Miss S. Findley, is $y = -20.6 + 0.39x - 0.000068x^2$, and the 5% confidence

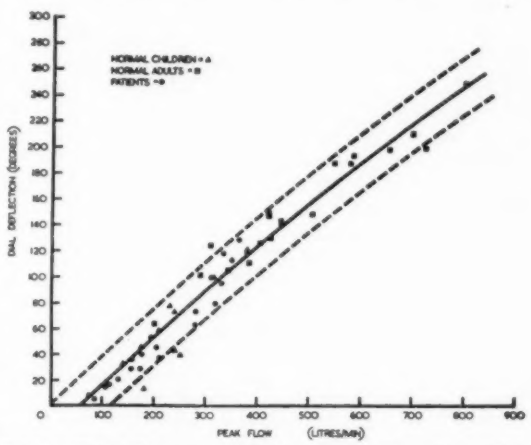

FIG. 6.—Calibration curve of prototype peak flow meter, using human subjects.

limits are as shown on the graph. It will be noted that the points for the different types of subject tend to be grouped together, but the error resulting from assuming that the points are homogeneous is not large.

A curve of this form was used to prepare a dial reading directly in litres per minute peak expiratory flow rate, as shown in Fig. 2.

The instrument has now been in commercial production in various forms for about two years. When the final design incorporating the new dial had been in production for about three months, two instruments were taken from stock and rechecked against the pneumotachograph, using exactly the same procedure as before, except that a rather smaller number of subjects were used and the patients were different. Fig. 7 shows the results for one instrument, and it can be seen that the agreement is satisfactory. The results for the other

instrument were so similar that they have been omitted for the sake of clarity.

A batch of 100 instruments were made at an early stage for a nation-wide survey of bronchitis organized

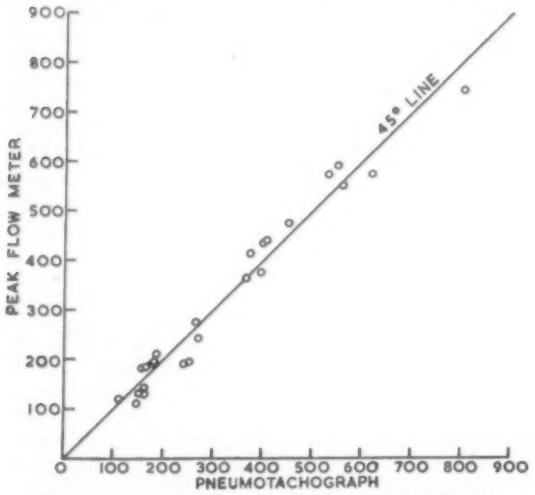

FIG. 7.—Recheck calibration on production instrument.

by the College of General Practitioners. Many of these were rather unsatisfactory, owing to "teething troubles," but the faults were mainly mechanical and did not affect their calibration. The stability of this is illustrated in the Table, which shows single readings taken on 17 subjects with six instruments which had been in use for a year. (We are indebted to Dr. C. M. Fletcher for these figures.)

Peak-Flow-Meter Readings in Litres per Minute

Subject	Instrument Number					
	107	125	135	158	173	217
1	780	780	770	760	740	780
2	820	750	780	760	760	740
3	730	690	720	700	690	670
4	730	640	680	620	640	610
5	490	470	450	420	440	440
6	440	430	430	380	420	420
7	750	740	720	700	700	680
8	620	600	660	600	600	560
9	490	460	440	400	440	430
10	530	530	550	500	530	550
11	740	690	680	700	650	640
12	590	600	570	560	550	520
13	152	136	140	140	112	120
14	190	164	170	180	147	140
15	450	420	460	430	440	400
16	320	300	290	320	310	310
17	120	140	130	130	100	120
Mean ..	526	501	508	488	486	478

Clinical Value of P.F.R. and Relation to Other Tests

It is not the purpose of this paper to enter into a detailed account of the clinical use of the instrument, because our experience of its use in this way has been rather limited.

The prototype instrument was constructed in 1954, and since that time has been used continuously by Dr. C. M. Fletcher, of the Postgraduate Medical School, London, for clinical and survey work. Another early model of the instrument has been used in several surveys conducted by the Pneumoconiosis Research Unit; an account of one of these has been given by Higgins (1957).

Using an early but quite satisfactory model of the instrument, Higgins carried out some extensive studies amongst a normal population in an agricultural district. In a restricted group of males aged 55 to 64 he found that the correlation coefficient between the P.F.R. and the F.E.V. (0.75 sec.) was 0.86, and he also obtained figures for the distribution of normal values for men and women aged from 25 to over 65 years. These figures are of interest for comparison with those quoted earlier which were given by other workers using other methods, but two points must be borne in mind. (1) As the instrument he used was an early model it had not been calibrated against actual peak flows. The figures he quotes were obtained by using the steady-flow calibration, which was quite consistently 17% too low. His figures, therefore, have all been multiplied by 1.17 to convert them to true peak flows. (2) The population he studied was a sample of a complete population and so included a number of disabled persons. Even so, the average value for males aged 25 to 34 with no history of exposure to dust was over 700 l./min. About 25% have P.F.R.s over 800 and about 3% over 900 l./min. At the other end of the scale, he recorded flows below 50 l./min. in very disabled elderly women, but otherwise flows below 100 l./min. were uncommon.

The only data at present available for children (given in Fig. 6) suggest that they can produce flows over 100 l./min. as soon as they will co-operate sufficiently to give reproducible results—that is, usually at about 4 years of age.

Initially, the P.F.M. was looked upon as a more convenient but substandard method of measuring the F.E.V., which in turn is usually regarded as bearing the same sort of relationship to the M.V.V.

An attempt was made to study directly the relationship between the peak expiratory flow rate and the M.V.V., but the results were not very satisfactory. Since then the use of the M.V.V. has been practically abandoned by the Pneumoconiosis Research Unit, so no further opportunity of carrying out a direct correlation study has occurred.

Meanwhile, however, it has become apparent that the P.F.R. is quite a stable and reproducible measurement—so much so that it has been customary to check both the P.F.M. and the pneumotachograph by using the known values of subjects who have had a reasonable amount of practice.

As a result, the relationship of the test to others such as the M.V.V. or the F.E.V. has become of less interest. It is obvious that no single factor can be used to translate the P.F.R. into the M.V.V., any more than the same can be done for the F.E.V., although numerous attempts have been made to do so.

In this paper, therefore, the P.F.M. is put forward as a simple and reliable device for measuring the maximum expiratory flow rate during a forced expiration, which in turn is put forward as a stable and useful measure of ventilatory capacity. Only clinical experience can eventually decide whether it is as generally useful as the M.V.V. or F.E.V., or whether, if it is not, its lesser usefulness is to some extent compensated for by the greater simplicity and portability of the instrument used for measuring it.

Summary

The advantages of the maximum forced expiratory flow rate as a measure of ventilatory capacity are

considered and the history of the use of the measurement is reviewed.

A new instrument, the peak flow meter, for making the measurement is described, and an account given of the method of calibration.

The available figures for the range of normal values are reviewed, and it is noted that the figures obtained with the peak flow meter are much higher than those recorded by most previous observers using other methods.

It is suggested that the maximum forced expiratory flow rate ("peak flow rate") measured with the peak flow meter may be found to be a convenient and reliable way of estimating ventilatory capacity.

This instrument has been developed over a period of several years, and it is impossible to acknowledge the help of all those who have assisted us. We should, however, specially like to thank the following: Dr. J. C. Gilson and the staff of the Pneumoconiosis Research Unit who have assisted in innumerable ways, including offering themselves and their children as subjects on a number of occasions; Mr. V. Gubb, who made two of the early models; and Messrs. Fred Ferraris, who started commercial manufacture and contributed a number of useful features to the design. Mrs. M. McDermott gave much valuable advice and assistance on the physical problems involved in the testing of the apparatus. The calibrations against the pneumotachograph were carried out by Miss M. Collins and Miss P. Edwards, and the drawings were made by Mr. C. W. Couling, Miss M. B. Wilson, and Miss M. Jenkins. Finally, we thank Dr. C. M. Fletcher for arranging numerous clinical trials of the instrument and for his constant help and encouragement. The instrument is distributed by Messrs. Airmed Ltd., of 16, Wigmore Street, London, W.1, who also supplied the photograph.

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Ten scholarships have been awarded this year by the British Commonwealth Nurses War Memorial Fund, bringing the total awarded since the Fund was founded in 1946 to 94. Four of this year's scholarships go to nurses of the United Kingdom, and six to Commonwealth countries: Canada, New Zealand (two), India, Rhodesia and Nyasaland, and Malta. The four United Kingdom awards go to Miss ANNIE ALTSCHUL (principal sister tutor, Bethlem Royal and Maudsley Hospitals, London), Miss CHARLOTTE BENTLEY (general secretary, National Association of State Enrolled Assistant Nurses), Mr. C. SCOWCROFT (principal tutor, Pinderfields General Hospital, Wakefield), and Mr. O. HUGHES (deputy chief male nurse, Bexley Hospital, Kent).

CASE OF CONN'S SYNDROME

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The syndrome of potassium depletion and hypertension due to adrenocortical adenoma was first described by Conn (1955a, 1955b). It is characterized clinically by episodes of severe muscle weakness and paralysis, intermittent tetany, and paraesthesiae. Hypertension is the rule, polyuria and polydipsia generally occur, but there is no oedema. The principal biochemical features are hypokalaemia and a varying degree of alkalosis and hypernatraemia. An increased secretion of aldosterone can often be demonstrated, and Conn named the syndrome primary aldosteronism. There is selective impairment of urinary concentration and acidification, and histologically a distinctive tubular vacuolation results from hypokalaemia. An increased liability to urinary infection often leads to progressive renal damage.

About 20 cases have been reported in which an adenoma was found either at operation or at necropsy (Conn and Louis, 1956; Mader and Iseri, 1955; Eales and Linder, 1956; Chalmers *et al.*, 1956; Hellem, 1956; Campbell *et al.*, 1956; Milne *et al.*, 1957; Skanse *et al.*, 1957; Hewlett *et al.*, 1957; Russell *et al.*, 1956, 1957; Fine *et al.*, 1957; Brooks *et al.*, 1957; Kretchmer *et al.*, 1957; Crane *et al.*, 1956, 1958). In two other cases the syndrome was produced by adrenocortical hyperplasia (Wyngaarden *et al.*, 1954; van Buchem *et al.*, 1956) and in two patients a malignant adrenocortical tumour was found (Foye and Feichtmeir, 1955; Brooks *et al.*, 1957). In the following case of Conn's syndrome no increase in aldosterone production could be demonstrated and a firm diagnosis could not be made before operation.

Case History

A spinster aged 47 had several attacks of urinary infection at the ages of 20 and 33. Thereafter she remained well until February, 1955, when at the age of 45 she noted increasing lethargy and nocturnal frequency of micturition. In September, 1955, she developed severe weakness, affecting the legs particularly, with lumbar pain and paraesthesiae in the arms.

She was thought to have poliomyelitis, and was admitted to a fever hospital, where she showed photophobia, and tenderness and paralysis of the leg muscles with absent reflexes. Her blood pressure was 180/100. The illness proved atypical, with normal cerebrospinal fluid and negative virological investigations. She made a spontaneous recovery after six weeks and was discharged. Her lethargy, however, continued and she remained liable to recurrent episodes of weakness in the legs, and in May, 1957, a severe exacerbation occurred after a respiratory infection. She was admitted to the Bolingbroke Hospital, where the hypokalaemia was discovered. Serum electrolyte levels on admission were: potassium, 2.6 mEq/l.; sodium 142 mEq/l.; chlorides, 102 mEq/l; alkali reserve, 32 mEq/l. She was very anaemic, with an Hb of 31%

and a macrocytic blood picture. Examination of the sternal marrow and a histamine test meal showed the changes of pernicious anaemia and she responded promptly to treatment with cyanocobalamin. In the nervous system there was generalized hypotonia, with weakness and tenderness in the legs and absent knee and ankle reflexes. The heart was normal apart from a basal systolic murmur, and the blood pressure was 150/90. An E.C.G. showed typical hypokalaemic changes.

Over the next 24 hours she was given 250 mEq of potassium as a mixture of potassium chloride and citrate by mouth. Her strength returned and the reflexes became normal. Subsequently she remained well with a potassium supplement of about 130 mEq daily, the serum potassium ranging from 3 to 4.4 mEq/l., but her symptoms returned if the supplement was withdrawn for more than three days.

In December she developed severe headache, became disorientated, and lapsed into a coma over a few hours. She was readmitted to the Bolingbroke Hospital and showed meningeal irritation and a right hemiparesis. She remained semicomatose for 10 days, and food and the potassium supplement were given via a Ryle tube. She eventually made a good recovery, but in January, 1958, whilst in the Westminster Hospital she developed an acute febrile illness followed by confusion and meningitis. The cerebrospinal fluid pressure was 240 mm., with a protein content of 60 mg./100 ml. and pleocytosis (polymorphs 100/c.mm., lymphocytes 40/c.mm.). Culture of the fluid was sterile. There were no localizing signs in the nervous system and she recovered fully in six days.

A month later she once again became confused, with severe dysphasia, followed by a Jacksonian convulsion, which started in the right hand and became generalized. Once again she made a rapid recovery and no further neurological episodes occurred. These incidents were thought to be cerebrovascular, probably thrombotic, and left carotid arteriography showed evidence of cerebral arteriosclerosis.

Metabolic studies were begun in February while she was on her potassium supplement of 130 mEq daily. Examination at this stage showed no weakness and no depression of the reflexes. Mild generalized cutaneous pigmentation was noted, not involving the mouth. There was residual nominal aphasia and slight visual defect in the right temporal field. She showed a labile hypertension, ranging from 130/90 to 220/160 and averaging 175/105. The only evidence of hypertensive heart disease was slight cardiac enlargement. E.C.G.s showed hypokalaemic changes only.

Investigations

Serum Electrolytes.—Serum potassium: Without supplements this was 2.5–2.8 mEq./l. On supplements it rose to low normal figures, but only 4 out of 29 pre-operation readings were over 4 mEq/l., the highest being 5.1 mEq/l. When given enteric-coated tablets of potassium chloride these were not absorbed and the serum potassium fell from 4 to 2.6 mEq/l. in three days. When potassium supplements were stopped after prolonged repletion the serum potassium fell from 4.6 to 2.8 mEq/l. in four days with a calculated negative balance of 180 mEq over this period. Serum sodium, 135–150 mEq/l. (average 145 mEq/l.). Serum chloride 96–110 mEq/l. (average 106 mEq/l.). Alkali reserve, 23–34 mEq/l. (average 28 mEq/l.). Serum calcium, 10.3 mg./100 ml. Serum phosphate, 4.3 mg./100 ml. Serum magnesium, 1.9 mg./100 ml. Blood urea, 14–35 mg./100 ml.

Urine.—Numerous catheter specimens of urine were examined. All showed mild to moderate albuminuria. Occasional specimens showed hyaline and granular casts. All were sterile save one specimen in May, 1957, which grew *Escherichia coli*.

Renal-function Tests.—24-hour urine volume over 10-day period on 230 mEq of potassium intake, 2–3.4 l. (average 2.6 l.). Urine concentration (12 hours), 1020. Urine dilution, 1001. 90% of 1,140 ml. water load (20 ml./kg.) excreted in four hours. Urinary reaction to litmus: generally neutral, occasionally acid or alkaline. Urinary *p*H after 5 g. of ammonium chloride orally:

	4–6 hours	6–9 hours
Pre-operative	7.4	6.8
Post-operative	5.9	5.9

Renal response to "pitressin": (pitressin tannate in oil 5 units intramuscularly):

	Urine flow	S.G.
0– 2 hours	3.5 ml./min.	1005
2– 4 hours	1.0 ml./min.	1011
4– 8 hours	1.5 ml./min.	1015
10–11 hours	0.5 ml./min.	1019

Urea clearance test, 66% average normal. Intravenous pyelogram, normal. Presacral pneumogram, normal renal and suprarenal outlines. Percutaneous renal biopsy (February 10, 1958): eight glomeruli were seen, and these and the vessels were normal; the tubules showed slight vacuolation only and in other respects were normal. At this time she had received a potassium supplement for eight months. Urinary aldosterone:—December 17, 1957: with potassium supplement (serum potassium 4.2 mEq/l.), 6.7 μg./24 hours; February 16, 1958: without potassium supplement (serum potassium 2.6 mEq/l., potassium intake 47 mEq/day), 1.8 μg./24 hours; March 30: post-operative (serum potassium 4.3 mEq/l., potassium intake 84 mEq/day), 0.3 μg./24 hours (normal range 3–7 μg./24 hours).

Urinary Steroid Excretion after Intramuscular A.C.T.H. ("*Corticotrophin Z*")

	Date	Dose of Corticotrophin (Same Batch)	17-ketosteroid Excretion (Mg./24 Hours)	17-hydroxysteroid Excretion (Mg./24 hours)
Pre-op.	18 1/58	Control	7·4	11·7
	19 1/58	,,	5·3	9·4
	20 1/58	20 units b.d.	7·2	11·8
	21 1/58	20 ,, ,,	3·3	7·0
	8 2/58	40 ,, ,,	4·8	11·5
	9/2/58	40 ,, ,,	6·6	14·3
Post-op.	8 4/58	Control	6·6	7·6
	9 4/58	,,	6·1	10·1
	10 4/58	20 units b.d.	8·2	26·2
	11 4/58	,, ,,	12·7	28·0

Glucose-tolerance test, normal. Liver-function tests and serum electrophoresis, normal. Faecal fat estimation (mean of five days), 5.7 g./24 hours. Sodium/potassium ratios were as follows:

	Daily Potassium Intake	Sodium/ Potassium Ratio	Flow Rate
Saliva:			
Pre-operative	224 mEq	0·9	0·8 ml./min.
	47 ,,	1·6	3·4 ,,
Post-operative	84 ,,	2·3	2·9 ,,
Faeces during balance studies:			
Pre-operative	47 mEq	0·5	
Post-operative	84 ,,	0·6	

Renal Potassium Excretion.—Daily potassium excretion related to potassium intake and serum potassium level is shown in Fig. 1. In potassium depletion, when the serum potassium is less than 3 mEq/l., the normal kidneys excrete less than 15 mEq/day. In our patient much higher values were obtained, and, for given levels of the serum potassium, excretion rates rose with the potassium intake, though on high intakes positive potassium balance was achieved. Three of the values on a potassium intake of 86 mEq daily were not conspicuously abnormal, and this may be due to the marked sodium retention over this period when a low-sodium diet was given (27 mEq/day). The fourth value is very abnormal, and this high excretion of potassium (175 mEq/day) was accompanied by sodium diuresis (100 mEq/day) following a convulsion (Day 54, Fig. 2).

Balance Data.—The response to high and low potassium intakes was studied in the pre-operative period (Fig. 3). During the first period of 14 days, on a potassium intake of 224 mEq/day, a positive potassium balance of about 820 mEq was achieved. Sodium balance was negative by 180 mEq on the fifth and seventh days of the study, but later became positive. During the second period of five days on a potassium intake of 47 mEq/day there was a negative potassium balance of 88 mEq and a positive sodium balance of 350 mEq. On the 12th post-operative day a further full balance was carried out over five days. On the first day of this balance the total exchangeable potassium measured with radio-potassium was 1,694 mEq (31.4 mEq/kg.). The potassium intake was 84 mEq daily and a positive balance of 70 mEq resulted. Sodium intake was 86 mEq daily and a negative sodium balance of 185 mEq occurred.

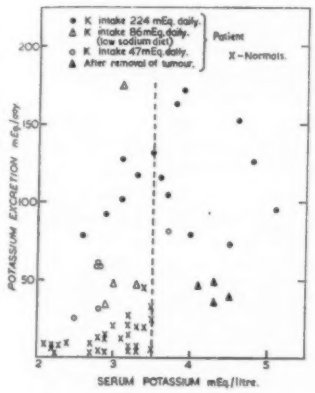
K intake 224 mEq. daily.
K intake 86 mEq. daily. (low sodium diet)
K intake 47 mEq. daily.
After removal of tumour.
Patient
X = Normals.
POTASSIUM EXCRETION mEq/day
SERUM POTASSIUM mEq/litre.

FIG. 1.—Relation between serum potassium levels and daily urinary potassium excretion. Normal data for urinary potassium loss, at serum potassium levels of 3.5 mEq/l. and lower, from the papers of Black and Milne (1952), Schwartz and Relman (1953), Evans *et al.* (1954), and Fourman (1954).

Response to Low Sodium Intake.—A diet containing 27 mEq of sodium and 86 mEq of potassium was given for 10 days. Urinary electrolyte excretion was as follows:

Day:	1	2	3	4	5	6	7	8	9	10
Urinary sodium (mEq/day)	60	18	18	4	2	13	19	100	30	4
,, potassium ,,	82	88	49	65	56	47	54	175	34	46

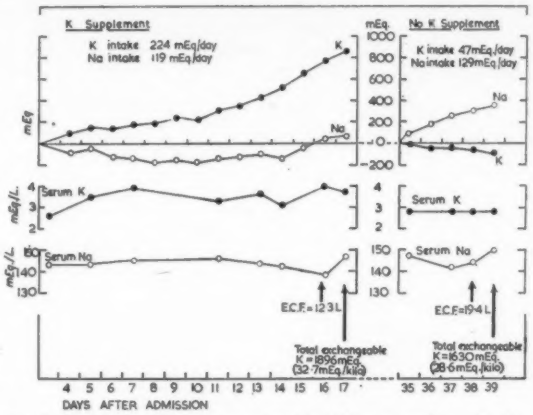

FIG. 3.—Balance data over two periods before operation. In the first period it was estimated that 90% of the patient's food was taken and a daily faecal loss of 30 mEq potassium and 10 mEq sodium was assumed. Total exchangeable potassium measured with radio-potassium and extracellular fluid volume with radio-bromine. Between days 17 and 35 she became ill and took little food. Despite continuing the potassium supplement, further potassium depletion occurred, partly explaining the marked increase in extracellular fluid volume.

There was marked sodium retention, with an average urinary sodium excretion of 19 mEq/day in the first week. On the eighth day the convulsion occurred, but, following this, sodium excretion fell again to low figures.

Management

The abnormal renal potassium loss was readily demonstrated, but it was uncertain whether this was due to Conn's syndrome or to potassium-losing nephritis. The absence of pyelonephritic changes in the renal biopsy favoured Conn's syndrome, but no increase in urinary aldosterone excretion was found, nor could an adrenal tumour be demonstrated radiologically. There was no hypernatraemia or alkalosis, and the electrolyte composition of saliva and faeces was normal. Furthermore, the previous

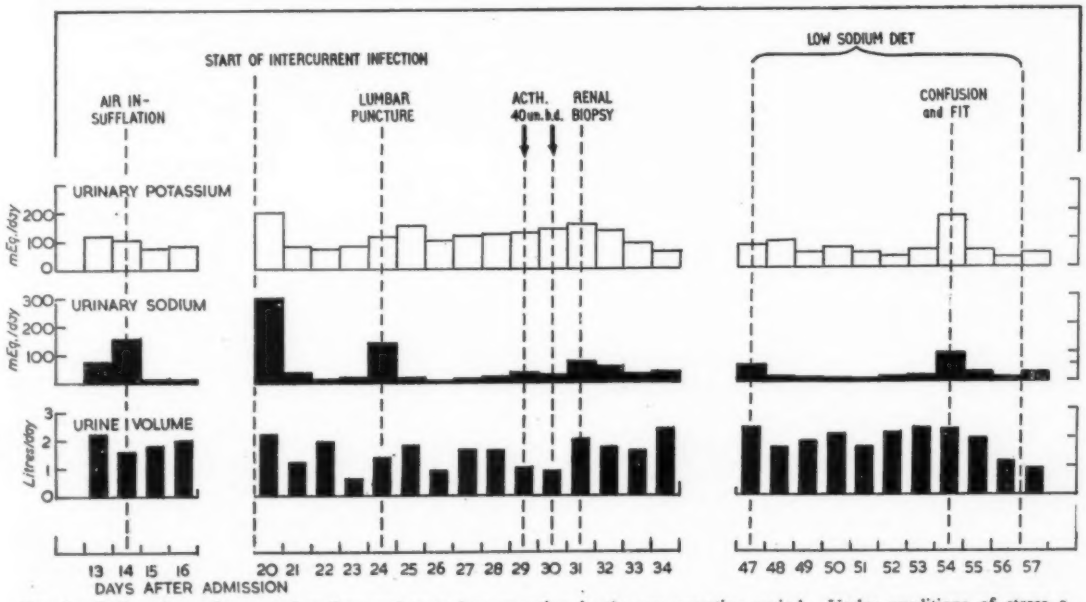

FIG. 2.—Daily urine volumes and sodium and potassium excretion in the pre-operative period. Under conditions of stress a marked sodium diuresis is seen, accompanied on one occasion (following convulsion) by a potassium diuresis. It is suggested that this represents a paradoxical response to increased adrenocortical activity.

history of urinary infection and positive culture on one occasion favoured pyelonephritis.

The investigations were therefore equivocal, but further neurological incidents seemed probable if the hypertension was not controlled, and an adrenal exploration was performed on March 14, 1958. This was done under a cortisone cover, as bilateral subtotal adrenalectomy was planned if no tumour was found. The left adrenal was inspected first by a postero-lateral approach. The gland was enlarged, and on removal was seen to be largely replaced by a round encapsulated tumour with a striking orange colour on transection. The gland weighed 22 g. and the tumour was 1 in. (2.5 cm.) in diameter. The left kidney appeared normal; no further biopsy was taken, and the right suprarenal was not examined.

The histology showed a benign cortical adenoma closely resembling those reported in other cases (Fig. 4). The cells were polyhedral, with rather vacuolated cytoplasm and well-defined round nuclei. The tumour appeared to be composed

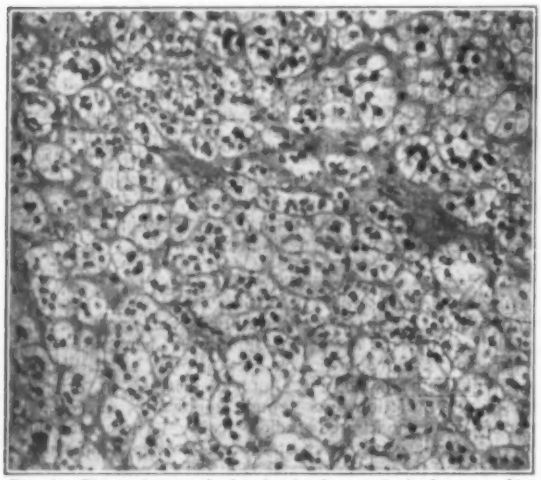

FIG. 4.—Photomicrograph showing benign cortical adenoma. The cells are polyhedral, with vacuolated cytoplasm and well-defined rounded nuclei. Appearances suggest that the adenoma is formed of cells predominantly from the zona fasciculata and resemble closely those of other reported cases of Conn's syndrome. The adrenal remnant showed no atrophy of the cortical zones.

predominantly of cells from the zona fasciculata. Sections from the adrenal remnant showed no significant abnormality.

After operation the patient remained well on a normal diet without potassium supplements. The serum potassium rose to 5.6 mEq/l. on the fourth post-operative day and thereafter fluctuated between 4.1 and 4.5 mEq/l. There was no change in serum sodium, chlorides, alkali reserve, or blood urea. Urinary potassium loss was high until the fourth post-operative day, when potassium supplements were stopped and the cortisone was gradually withdrawn. The blood pressure fell and fluctuated between 120/70 and 180/100, averaging 140/90. Renal acidification rapidly improved, but concentration remained unaffected. She has been followed up subsequently in the out-patient department and remained well apart from difficulty in reading and writing. The blood pressure after four months was 145/105, and after six months was 135/80. The E.C.G. is normal and serum electrolyte levels have all been normal. The values six months after operation were: sodium, 144 mEq/l.; potassium, 4.7 mEq/l.; chlorides, 108 mEq/l.; alkali reserve, 33 mEq/l.; urea, 41 mg./100 ml.

Discussion

The diagnosis of Conn's syndrome in our patient is justified by the reversal of potassium depletion and amelioration of hypertension which followed removal of a typical adrenal adenoma. There are, however, several unusual features which prevented a confident initial diagnosis.

The long history of urinary infection was misleading until the results of repeated urine examination and the renal biopsy showed little evidence of pyelonephritis. Paraesthesiae occurred only in the first episode of weakness and she never showed tetany. She did not complain of polyuria or polydipsia, though daily urine volumes were large and occasional nocturnal frequency occurred which subsided after operation.

The changes in serum electrolytes were also unusual, and hypokalaemia was the only abnormality. She never showed hypernatraemia or alkalosis, though these features are sometimes absent in Conn's syndrome. There was no fall in the serum magnesium (Mader and Iseri, 1955; Milne *et al.*, 1957), and no reduction in the serum phosphate, which may occur as a secondary effect of potassium depletion (Mahler and Stanbury, 1956). She did not show hyperglycaemia and glycosuria as reported in the cases of Hewlett *et al.* (1957). Urinary aldosterone excretion was also misleading. The first estimation (6.7μg/24 hours) was during high potassium intake when the serum potassium level was normal, and could be interpreted as a normal suprarenal response. The second estimation (1.8 μg./24 hours) was below the normal range and is a very unusual finding. The marked reduction in urinary aldosterone excretion post-operatively (0.3 μg./24 hours) does, however, suggest that most of the excreted aldosterone was formed by the tumour. Normal values for this hormone in the urine have been reported in three other cases (Milne *et al.*, 1957; Russell *et al.*, 1957; Brooks *et al.*, 1957), and in a fourth was normal on two out of three occasions (Chalmers *et al.*, 1956). Only a small proportion of aldosterone formed in the body can be recovered from the urine, and the aldosterone content of the tumour in our patient has not been assayed. We are therefore unable to decide whether excessive aldosterone production occurred in our case and have avoided the term primary aldosteronism for this reason.

The electrolyte composition of saliva and faeces was also unusual, and well within the normal range. It has been shown by Pawan (1955) that a marked variation in salivary sodium/potassium ratios (0.15–2.10) may occur in normal subjects depending on diurnal variation and rates of flow.

The urinary findings, on the other hand, were suggestive of Conn's syndrome. A positive culture was obtained on an isolated occasion only and renal function was good, apart from selective impairment of concentration and acidification due to kalopenic nephropathy. The renal biopsy was also helpful in showing tubular vacuolation only. It must be remembered, however, that pyelonephritis may be focal, and that the small fragment obtained at renal biopsy may not be representative of the kidney as a whole. Conversely, even if severe pyelonephritis is found this may be a secondary development in Conn's syndrome.

Bartter (1956) has suggested that urinary sodium excretion during sodium restriction is important in differentiating Conn's syndrome and potassium-losing nephritis. Patients with Conn's syndrome should excrete urine with a minimal sodium content, whereas in

potassium-losing nephritis a salt-losing tendency may be unmasked, though this may also occur in Conn's syndrome when renal damage has occurred (Mader and Iseri, 1955; Milne *et al.*, 1957). Mahler and Stanbury (1956) have shown that severe potassium depletion itself may impair sodium retention, and in our patient the response to sodium depletion was studied after potassium supplements had been given, so that the potassium deficit at this time was probably small. Urinary sodium excretion fell promptly and over the first seven days averaged 19 mEq daily on a sodium intake of 27 mEq daily.

Renwick *et al.* (1955) found no difference between hypertensive and normotensive subjects in their response to sodium restriction and noted that seven to nine days were required before urinary sodium excretion became restabilized at a low level, and Hatch (1954) found the period of restabilization extended over three weeks. The low average daily sodium excretion in our patient in the first week of sodium restriction is striking, and may be contrasted to the average daily sodium excretion in a hypertensive subject (38 mEq daily) and a normotensive subject (39 mEq daily), both free from renal disease and heart failure, in their first week on a similar diet. This suggests that in Conn's syndrome sodium retention may be excessive on a low sodium intake, but further observations are required to confirm this.

Conn (1955a) noted a paradoxical response in electrolyte excretion when corticotrophin was given to his patient. The effect was delayed until the third day, when a heavy sodium diuresis occurred. Our patient was given corticotrophin for two 48-hour periods by the intramuscular route as the veins were poor. No change in electrolyte excretion occurred, but estimation of urinary steroids showed that the corticotrophin had produced no adrenal response. Post-operatively an increase in steroid excretion occurred with 20 units of corticotrophin b.d., and the initial failure to respond to 40 units of corticotrophin b.d. of the same batch is rather surprising. Our patient did show, however, a sodium diuresis whenever subjected to stress. The response occurred on the same day and was generally accompanied by an increase in potassium excretion. This is demonstrated in Fig. 4 accompanying air insufflation, the start of an intercurrent infection, lumbar puncture, renal biopsy, and a convulsion. Mader and Iseri (1955) obtained a similar immediate sodium diuresis, with increased potassium excretion by giving 25 mg. of cortisone intravenously to their patient. This curious response to stress in our case may therefore be a paradoxical effect of increased adrenocortical activity.

The diagnostic problems in Conn's syndrome may be considerable. Excessive renal potassium loss occurs in renal tubular acidosis, the Fanconi syndrome, and following uretero-sigmoidostomy. These conditions are all associated with acidosis and a low serum bicarbonate level, and are readily distinguished. The distinction between Conn's syndrome and potassium-losing nephritis, however, may be very difficult. In patients such as ours, even when renal damage is slight, the diagnosis may only be presumptive when biochemical changes other than hypokalaemia are absent, and when no evidence of an adrenal tumour or increased aldosterone production can be demonstrated. These investigations are of little value if negative, and in these circumstances the discovery of excessive sodium retention following sodium restriction, and an abnormal electrolyte excretion in response to stress, may be of help.

When pyelonephritis is present the distinction between Conn's syndrome and potassium-losing nephritis may be impossible before operation. The demonstration of increased urinary aldosterone excretion may be of no help at this stage, since chronic pyelonephritis may lead to adrenal hyperplasia and secondary aldosteronism (Luetscher, 1956). Furthermore, secondary aldosteronism may occur in the late stages of hypertension, and potassium depletion with increased aldosterone production, mimicking Conn's syndrome, has been reported by FitzGerald *et al.* (1957) in a case of malignant hypertension. With the present diagnostic methods it appears that an adrenal adenoma can be excluded with certainty only by exploration of the adrenals.

Most cases of Conn's syndrome are progressive, with increasing hypertension and secondary renal damage. Conn (1955a, 1955b) quotes two cases in which the patients died; and the patient of Brooks *et al.* (1957) died after being hypertensive for 15 years. On the other hand, removal of the tumour arrests the process, though hypertension has recurred later in some cases. In the absence of acidosis or severe impairment of renal function, the demonstration of progressive urinary potassium depletion in a hypertensive patient seems an indication for planned exploration of the adrenals. If severe renal damage is already present removal of a tumour or hyperplastic adrenals may precipitate renal failure, as a decrease in renal function may follow operation (Chalmers *et al.*, 1956; van Buchem *et al.*, 1956; Dustan *et al.*, 1956; Milne *et al.*, 1957).

Summary

A case is described of Conn's syndrome due to a benign adrenocortical adenoma. The patient suffered from recurrent episodes of severe muscular weakness and showed marked hypokalaemia without hypernatraemia or alkalosis.

Renal-function tests showed selective impairment of urinary concentration and acidification. Renal biopsy showed slight tubular vacuolation only. No adrenal tumour was demonstrated by air insufflation and no increase in urinary aldosterone excretion was found.

Balance data are given and an excessive renal response to sodium restriction is described. A paradoxical response to stress was noted, with increased urinary sodium loss and a less constant potassium diuresis.

The problems of diagnosis are discussed. At present the distinction from potassium-losing renal disease may be made only at operation.

We thank Dr. R. E. Rodgers for permission to publish this case, and Dr. R. I. S. Bayliss, under whose care the patient was later admitted, for his advice in the preparation of this paper. The adrenalectomy was performed by Mr. Robert Cox. The urinary aldosterone assays were estimated by Professor F. T. G. Prunty and Dr. R. V. Brooks. The serum magnesium level was estimated by Dr. I. McIntyre. Isotope studies were performed by Dr. J. P. Nicholson and Dr. J. F. Zilva. The histological study

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of the tumour was made by Dr. D. A. H. Mackenzie. The illustrations were prepared by Miss Jeannette Purkiss.

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Every year fire brigades in the United Kingdom attend about 500 fires in such places as nursing-homes and hospitals of all kinds, clinics and welfare centres, children's and old people's homes, special schools for handicapped children, day nurseries, training centres for ex-Service men, and institutions for the blind. . . . Generally speaking the causes of most of the fires were not peculiar to hospitals but were similar to those of fires in dwellings. Many were the result of carelessness or forgetfulness—for instance, 18 were due to dropped smoking materials, and of these five were started by people who were smoking in bed. An important proportion of fires was concerned with cooking and heating equipment. . . . Six fires originated in hospital boilers or furnaces and seven were caused by chimneys or flues. Two fires arose as a result of a fairly common practice in hospitals—shielding the glare from an electric lamp by draping a cloth or towel round it; and one fire was started by the flame from a lighted sulphur fumigating cone placed on a mattress. Only five of the fires were peculiar to hospitals in that they involved special hospital equipment. There were three fires in sterilizers, two electric and one gas-heated, and the two other fires originated in immersion heaters in *x*-ray developing tanks. One of the most encouraging conclusions of this survey is that the provision of fire-fighting equipment seems to have been adequate, and most of the fires were tackled by the hospital staff, who were able to extinguish 52 of them without fire brigade assistance. . . . (*Fire Protection Association Journal*, July, 1959.)

A CONTROLLED TRIAL OF IMIPRAMINE IN TREATMENT OF DEPRESSIVE STATES

BY

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Imipramine, an iminodibenzyl derivative, is a distant relative of chlorpromazine. Investigation of this substance was carried out by Kuhn, at Munsterlingen, in 1950, but after an initial and limited assessment it was put aside until interest was rekindled in 1954 after the beneficial effects of chlorpromazine had been established (Kuhn, 1957). Like iproniazid, imipramine inhibits the lowering of the serotonin level in the brain caused by reserpine (van Meter *et al.*, 1959). A number of clinical studies published on the effects of imipramine suggest that the drug is of considerable value in the treatment of depression and that its effects are at least comparable to those of electric convulsion therapy (E.C.T.).

In three years Kuhn (1957, 1958) treated 500 patients suffering from various psychiatric disorders with imipramine. The best results were obtained in endogenous depression, and he states that success can be expected in three-quarters to four-fifths of cases. In reactive depression a significant though less marked response was noted.

Kielholz and Battegay (1958) treated 69 cases of severe depression and found that 67% were improved or became symptom-free.

Lehmann *et al.* (1958) reported the effects of imipramine upon 84 patients in whom depression was a prominent feature. Three-fifths of these suffered from endogenous depression. Within eight weeks 60% had recovered or were much improved.

Fazio *et al.* (1958) found that in 50 cases of depression of varied aetiology 32% showed a full clinical remission and 42% were appreciably improved. Imipramine appeared to be most effective in recurrent depression.

Straker (1959) treated with imipramine 26 patients from his private practice mostly suffering from endogenous depression: 80% recovered or were "vastly improved."

Sloane *et al.* (1959) selected 30 patients—the majority suffering from endogenous depression—who would otherwise have been given E.C.T.: 80% recovered, and the authors felt that the results were comparable to or even somewhat better than those of E.C.T. An abortive attempt to carry out a controlled trial on 12 patients was made, but it was terminated after two weeks and no useful conclusions could be drawn.

Mann (1959) gave imipramine to 70 cases of depression of various types and found that 63% recovered or were much improved: 40 cases were described as suffering from "neurotic depression," but this group included many involutional cases.

Azima (1959) used imipramine in 100 patients with depression. Of these, 44 suffered from psychotic depression, and 61.3% of this group showed a marked improvement and 29.5% were moderately improved. Of 38 cases of neurotic depression, 30.3% were greatly improved and 44.6% showed moderate improvement.

Delay *et al.* (1959) treated 137 cases of various forms of depressive disorder. The best results were obtained in cases of recurrent depression, of which 75% recovered or showed great improvement. In involutional melancholia, 67% of the cases responded to the same degree, and in "arteriosclerotic" depression 70% of cases showed a good result. The results were less impressive when the depression occurred as a feature of neurotic illness or in association with psychopathy.

Methods

The purpose of the present trial was simply to decide if imipramine was an effective agent in the treatment, firstly, of endogenous depression, and, secondly, of reactive depression. It is felt that endogenous depression and reactive or neurotic depression are distinct entities, and even though their separation is not always easy to make on clinical grounds this should be attempted in view of the wide differences in the response of the two groups to physical treatments and in their ultimate prognosis (Roth, 1959).

All the cases included in the trial were out-patients, and anyone showing gross retardation or extreme agitation and those in whom the risk of suicide was considerable were automatically excluded, as they were admitted for in-patient treatment. Nevertheless, a number of the patients included were quite severely depressed. One did commit suicide during the trial shortly after starting on the placebo. He was adamant in his refusal to come into hospital.

The clinical trial was organized in conjunction with the hospital dispensary, and cases were allocated at random to the active and placebo groups by the hospital pharmacist. On the first and second days of treatment four 25-mg. tablets were given; the dosage was increased to six, eight, and finally ten tablets daily by the fifth day. Patients were seen weekly, and this dosage was maintained for four weeks. If no improvement had occurred at the end of this period the drug was regarded as ineffective and some other form of treatment was instituted. In most cases the alternative tablets were given for a further period. The results of this crossover trial are not yet available and will be reported at a later date. Patients who responded to the tablets they were receiving were kept on these until maximal improvement was obtained. Without exception this occurred within six weeks of starting treatment. How long it is necessary to continue the administration of imipramine to avoid the risk of relapse has not yet been established.

With regard to preknowledge of what the patient was receiving before the code was broken, we had the usual hints from the side-effects that occurred. However, these proved to be a double-edged weapon—as shown below—and did not invalidate the trial in any degree.

The average age of the patients with endogenous depression was 50.2 years and of those with reactive depression 43.2 years. With regard to sex distribution, of 55 cases of endogenous depression 38 were female and 17 male. Of 42 cases of reactive depressions 26 were female and 16 male.

The results of treatment were assessed as symptom-free, greatly improved, somewhat improved, no change, or worse. For the purpose of assessing the value of the drug as a significant therapeutic agent, the first two of these categories have been combined as a good or worth-while result and the other three as a poor result. Patients showing a good result were able to return to their normal activities without undue effort.

Only the immediate results of treatment are reported in this paper, but the patients are being followed up, and it is felt that the results after three and six months may be of even greater interest.

Results

Of 55 cases of endogenous depression treated, 27 received imipramine and 28 the placebo. On imipramine 20 responded well, while 7 did badly. On the placebo, 6 did well and 22 badly. This is a highly significant difference, and, with Yates's correction applied, $P<0.01$.

Of the 42 cases of reactive depression 22 received imipramine and 20 the placebo. Of those given imipramine 13 were improved and 9 were not; while of the 20 controls 4 improved and 16 showed a poor result. This, too, is a significant result ($P<0.02$). When improvement occurred it was nearly always evident by the end of the third week, sometimes as early as the fourth or fifth day. The mean was 9 to 10 days.

Of the 27 cases of endogenous depression treated with imipramine 20 were females and 7 were males. Of the 20 women 14 did well, and of the 7 men 6 had a good result. Of the 22 cases of reactive depression given imipramine 9 out of 14 women did well, compared with 4 out of 8 men. Freyhan (1959) has suggested that women respond better to imipramine than men. These figures lend no support to this view.

Side-effects

Of the 49 cases on imipramine included in the trial, 27 had side-effects of one kind or another. These included dryness of the mouth, sweating, dizzy feelings, drowsiness, and nausea. Constipation was reported occasionally, as was difficulty in starting micturition. In none of these cases were the effects severe. The side-effects usually became evident during the first week of treatment and tended to improve or even disappear after two or three weeks. One patient, an intractable case of endogenous depression, who in the past had had repeated courses of E.C.T. and a prefrontal leucotomy with only transient benefit, improved rapidly on imipramine, but after three weeks entered a hypomanic phase, which has continued in spite of stopping the imipramine. She gave no history of previous manic swings. An urticarial rash occurred in one patient while taking imipramine, but was regarded as coincidental.

We have had no examples of jaundice resulting from the use of imipramine, though Delay *et al.* (1959) refer to such cases, which appear to have been mild and none fatal. One patient, after two weeks on imipramine, developed a severe diabetes mellitus and was taken off the trial. It is not possible to say with any assurance whether or not there was any causal connexion between the onset of the diabetes and the administration of imipramine. Two cases suffered haematemeses in the second week of treatment with imipramine. One, a man aged 61, died a few days later and was found to have a gastric carcinoma; the other patient is still under investigation. A third patient, noticed to be pale, was

admitted to hospital for investigation, and her stools gave a positive result for occult blood. No cause for this could be found. In these cases the imipramine was discontinued and they were not included in the trial.

Six further patients ceased to take their tablets after a few days because of intolerable side-effects and were therefore excluded. They complained variously of intense malaise and lethargy, weakness and dizziness, and of unsteadiness and palpitations. Of the six patients, four were taking imipramine and two the placebo. Two cases also excluded from the trial failed to keep their out-patient appointments, so that no further assessments were possible.

Of the 48 patients on the placebo tablets 13 showed side-effects, including dryness of the mouth, lethargy and drowsiness, dizziness, constipation, and diarrhoea. One of these also had an urticarial rash. These are what one might term negative placebo effects, and clearly form a safeguard in some degree against breakdown of the double-blind system.

Conclusions

This clinical trial of imipramine set out to decide whether or not the drug had a worth-while effect upon depressive illnesses. So far as endogenous depression is concerned, the trial shows that imipramine is an effective agent, 74% of cases showing a good response.

In a controlled trial involving 81 patients carried out in this department and at St. Nicholas' Hospital to evaluate the effect of iproniazid, 54% of cases of endogenous depression showed a good response. Although the groups of depressives included in the two trials are not strictly comparable—those treated with iproniazid were on the whole more severe—the suggestion emerges that imipramine is the more effective agent. Delay *et al.* (1959) obtained a similar impression. In a group of 137 cases of depression of various causes treated with imipramine, 60% recovered or were greatly improved. A similar comparable trial of iproniazid gave a figure of 47%.

As no group of patients treated with E.C.T. was included in the trial of imipramine, a direct comparison with this form of treatment cannot be made. In the iproniazid trial, E.C.T. gave a good response in 89% of cases, and it is likely that a similar figure would have been obtained had such a group been included in the imipramine trial. If so, it would suggest that, so far as the immediate effects are concerned, imipramine is somewhat inferior therapeutically to E.C.T. However, in view of the high relapse rate among patients treated with E.C.T., it does not follow that this superiority will be maintained after three or six months. Several cases included in the trial had previously had courses of E.C.T., and many of these appeared to respond equally well to imipramine. Only one case was included which might be described as resistant to E.C.T., and this, too, responded well. It has certainly been obvious in this department that since the introduction of iproniazid and imipramine the amount of in-patient and out-patient E.C.T. given has fallen sharply.

The drug treatment of depressive illness has many obvious advantages over E.C.T. However safe the latter has become, there can be no denial that as a method of treatment it is far more unpleasant than taking a few tablets. The drugs produce no confusion or disturbance of memory, which is a particular advantage for those whose work is primarily intellectual. It is possible for some patients to avoid losing work—an inevitable occurrence when out-patient E.C.T. is given—and where facilities for out-patient E.C.T. are not provided or are impracticable admission to hospital may be avoided. Nevertheless, adequate observation and supervision is necessary because of the toxic effects of these drugs as well as the continuing risk of suicide in some cases and the possibility that other forms of treatment may be required.

The side-effects in general are less disturbing than those associated with E.C.T. and on the whole are not serious. A possible danger is liver necrosis, but the frequency and severity of this appear to be less than in the case of iproniazid.

It seems to be well worth trying either iproniazid or imipramine in most cases of endogenous depression before deciding to give E.C.T. It is probably advisable to make exceptions of those cases in which there is a real danger of suicide, cases presenting in stupor or showing marked inanition, and those in which there is any suspicion of liver disease. It must be accepted that if depressive illness is treated with these drugs E.C.T. may still be necessary in a number of cases.

Imipramine appears to be of value also in reactive depression, and 59% of cases treated did well. Many of these cases, though relieved of their depression, continued to experience tension symptoms and other neurotic manifestations, which, however, usually proved much easier to bear than before. In view of the poor response of this group generally to E.C.T., this finding was somewhat unexpected and correspondingly more gratifying.

The real importance of these new antidepressive drugs appears to be twofold. Firstly, they provide an effective, easily administered, and readily acceptable form of treatment in most cases of depressive illness, which is one of the most important categories of mental disturbance with which the physician has to deal. Secondly, the modes of response to these drugs indicate lines of research which may well lead to the elucidation of the aetiological factors which play an immediate part in determining the onset of depressive illness. One feels hopeful that a study of the metabolism of these drugs and of their effect on the brain enzyme systems may well have far-reaching results, for it appears likely that they act upon what one might term the basic mechanisms in depression, and they are certainly more than euphorizing agents like the amphetamines.

Summary

A controlled trial was carried out to evaluate the effects of imipramine on endogenous and reactive depression.

In endogenous depression 74% of cases showed a good response to the drug, while 22% responded to the placebo ($P<0.01$).

In reactive depression 59% responded satisfactorily on imipramine, as compared with 20% on the placebo ($P<0.02$).

On comparing these results with those of a previous trial of iproniazid the impression was obtained that imipramine was the more effective agent in treating endogenous depression.

We thank our colleagues at the Royal Victoria Infirmary and at the Newcastle General Hospital for allowing us to include their patients in this clinical trial, and we are

pleased to acknowledge our indebtedness to Professor Martin Roth for his advice and encouragement. We are grateful to Geigy Pharmaceutical Company Ltd., who supplied the imipramine ("tofranil") and placebo tablets, and particularly to Dr. Alan Broadhurst for his valuable co-operation.

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CYCLOSERINE IN TREATMENT OF INFECTION OF URINARY TRACT

BY

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Cycloserine, first isolated in 1954 as a fermentation product of *Streptomyces orchidaceus* (Harned *et al.*, 1955), has been extensively investigated in the treatment of tuberculosis. Toxicity in patients given large doses for prolonged periods is the major disadvantage of such therapy (Walker and Murdoch, 1957). Nevertheless, lower oral dosage for short periods is virtually non-toxic provided renal function is good. Under these circumstances much higher urine than plasma concentrations are achieved (Welch *et al.*, 1955). Cycloserine has therefore been used to a limited extent, with encouraging results, in patients suffering from infections of the urinary tract caused by a variety of organisms (Herrold *et al.*, 1955; Hughes *et al.*, 1958). *In vitro* studies have also suggested that concentrations of cycloserine sufficient to inhibit the growth of some strains of coliform organisms are attainable in human urine (Welch *et al.*, 1955; Garrod, 1959). We report here the results of a detailed study of the use of cycloserine in a small number of patients with severe infection of the urinary tract by coliform organisms who have been observed for periods of two to seven months.

Materials and Methods

Clinical

Five female patients have so far been selected for study. Three were diabetic subjects who had suffered severe and repeated attacks of urinary infection characterized by malaise, frequency of micturition, nocturia, and dull loin pain for many months. Treatment with courses of sulphonamides, chloramphenicol, tetracyclines, and streptomycin had failed to relieve the symptoms or to render the urine sterile for an appreciable length of time. Renal biopsy was successfully performed in two of these three patients and histological evidence of pyelonephritis was demonstrated in both. Kidney tissue was not obtained from the third patient. The two remaining patients, who were not diabetic, had acute infections causing severe illness with high fever, rigors, dysuria, and oliguria of short duration. Renal biopsy was therefore not performed because of the delay involved in preparing for this procedure. Similarly, pre-treatment laboratory studies were also curtailed. Individual details of the patients are shown in Table I.

Treatment consisted of the daily oral administration of cycloserine in doses of 250 mg. eight-hourly for 14 days. Each patient was instructed not to drink excessively during this time. Daily observations of the temperature, pulse, and respiration rates and of the urinary volume were made. The patients were questioned and examined daily in respect of the subsidence or otherwise of their disease. Subjective and objective signs of drug toxicity, such as drowsiness, personality change, myoclonus, and epileptiform phenomena, were especially sought.

Bacteriological

As repeated catheterization carried with it the risk of introducing further infection, the following method of obtaining "clean" mid-stream specimens was devised. Patients were instructed to bathe in the early morning, washing the ano-genital region thoroughly with hexachlorophane soap. Urine was voided at 9 a.m. and discarded. Chlorhexidine cream was applied to the labia at 10.45 a.m. At 11 a.m. the patient, in the erect posture, with the labia separated by a sterile gloved hand, voided urine. The mid-urinary flow was collected in a wide-mouthed sterile jar and delivered immediately to the bacteriologist. Three such specimens were obtained on successive mornings before treatment was begun in Cases 1, 2, and 3. Only one such specimen was taken in Cases 4 and 5.

The pretreatment specimens from all patients were examined by standard laboratory procedures—namely,

TABLE I.—*Pretreatment Clinical Observations*

Case No.	Age and Sex	Duration	Temp. Rise	W.B.C. Cells/c.mm.	E.S.R. Westergren	I.V.P.	Renal Biopsy
1	27 F	12 months	97–100° F. (36·1–37·8° C.)	6,000	50 mm.	Normal	Failed
2	55 F	3 ,,	97–98·6° F. (36·1–37° C.)	7,000	42 ,,	,,	Acute pyelonephritis
3	38 F	12 ,,	97–99° F. (36·1–37·2° C.)	7,500	93 ,,	,,	Chronic pyelonephritis
4	24 F	1 month	99–105° F. (Rigors) (37·2–40·6° C.)	17,200	45 ,,	—	—
5	20 F	3 weeks	99–102·4° F. (37·2–39·1° C.)	10,600	45 ,,	—	—

microscopy of stained centrifuged deposit, culture on blood-agar and MacConkey-agar plates.

Microscopy showed the presence of large numbers of pus cells and Gram-negative bacilli. The cultures yielded pure and heavy growths of *Escherichia coli* in all five cases.

The antibiotic sensitivity pattern of these organisms was determined by the disk-diffusion method (Bowie and Gould, 1952). The minimum concentration of cycloserine required to inhibit the growth of these strains of *E. coli* was determined in the following manner. A standard solution of cycloserine was prepared by dissolving 100 mg. of the drug in 100 ml. of meat-extract broth. This was diluted appropriately, with broth, to give concentrations of cycloserine ranging from 1,000 to 25 μg./ml. 0.5-ml. aliquots of these solutions were inoculated with 0.02 ml. of a 1 in 250 dilution of an overnight broth culture of the organisms under test. The concentrations of cycloserine required to produce growth inhibition were noted after 18 hours' incubation at 37° C. (see Table II).

TABLE II.—*Resistance Pattern and Minimum Inhibitory Concentration of Cycloserine for the Causative Organism*

Case No.	Causative Organism	Disk Sensitivity Pattern					M.I.C. Cycloserine (μg. ml.)
		Su	P	Str	C	T	
1	E. coli	R	R	S	S	S	100
2	,,	S	R	S	S	R	125
3	,,	S	R	S	S	R	100
4	,,	R	R	S	S	S	100
5	,,	S	R	S	S	R	75

Su = Sulphonamide. P = Penicillin. Str = Streptomycin. C = Chloramphenicol. T = Tetracyclines. M.I.C. = Minimum inhibitory concentration.

The viable organisms in the three pretreatment specimens in Cases 1, 2, and 3 were enumerated (Miles and Misra, 1938).

During treatment, mid-stream specimens of urine from Cases 1, 2, and 3 were obtained on alternate days and submitted to the full laboratory procedures already described. In Cases 4 and 5 standard laboratory cultures were performed twice weekly.

Biochemical

The following studies of renal function were made on each patient on a number of occasions before and after cycloserine administration: (*a*) creatinine-clearance test, and (*b*) blood-urea nitrogen determination. The results of these studies are summarized in Table III.

During treatment cycloserine concentrations were measured (Jones, 1956) in plasma and in 24-hour collections of urine, every second day.

Results

All five patients responded dramatically to treatment. Within three days they were afebrile and free from all urinary symptoms, the most striking feature being the disappearance of nocturia. Patients 1, 2, and 3 had their first nights of uninterrupted sleep for many months. Patients 4 and 5, who had high swinging fever, sweating, and prostration, became afebrile within 48 hours after the start of treatment, and rapidly regained their appetite and feeling of well-being. All patients have remained completely well since stopping treatment, the follow-up periods ranging from two to seven months.

TABLE III.—*Renal Function Tests Before and After Treatment*

Case No.	Mean Blood-urea Nitrogen (mg. 100 ml.)		Serum Creatinine (mg./100 ml.)		Creatinine Clearance (ml. min.)	
	Before	After	Before	After	Before	After
1	19 (3)	20 (3)	1·1 (2)	0·7 (2)	50 (2)	64 (3)
2	15 (4)	15 (2)	0·75 (4)	0·7 (2)	102 (4)	77 (2)
3	41 (2)	55 (2)	1·8 (1)	1·5 (2)	33 (1)	40 (2)
4	16 (2)	—	0·7 (2)	0·6 (1)	92 (2)	64 (1)
5	14 (1)	9 (1)	0·6 (1)	0·6 (1)	45 (1)	144 (1)
Normal ranges ..	8–20		0·6–1·2		80–130	

Figures in parentheses indicate the number of determinations from which each mean value was derived.
Urea-nitrogen determinations by the manometric Van Slyke technique.
24-hour creatinine-clearance determinations by the method of Owen, Iggo, Scandrett, and Stewart (1954).

With one exception there was no evidence, either subjectively or objectively, of any toxicity attributable to cycloserine in the dosage employed. The patient (Case 3) who showed a mild personality change, characterized by phases of depression alternating with mild confusion, previously had impaired renal function (see Table III) and in consequence had much higher plasma cycloserine levels than the other patients in the series. These toxic effects, however, rapidly disappeared at the end of treatment and were never severe enough to warrant withdrawal of the drug.

Figs. 1, 2, and 3 illustrate the bacteriological progress in Cases 1, 2, and 3 respectively, in relation to the urine and plasma concentrations of cycloserine achieved during treatment. They also illustrate that the urinary concentrations attained equal or exceed the minimum inhibitory concentrations of cycloserine required for the strains of *E. coli* isolated from these patients. Cases 4 and 5 achieved urine cycloserine concentrations of 113 and 172 μg./ml. respectively, and these substantially exceeded the minimum inhibitory concentrations for their respective strains of *E. coli*. (see Table II).

In every case microscopical evidence of pyuria disappeared when the urine became sterile. Follow-up studies at approximately monthly intervals have shown no bacteriological evidence of relapse (see Figs. 1–3).

There has been no marked change in the results of the renal-function tests during the period of the study, with the exception of Case 5. In this instance the marked increase in creatinine clearance probably reflects an improvement in fluid balance rather than a change in glomerular filtration efficiency.

Discussion

The treatment of recurrent infection of the urinary tract in women is notoriously difficult, and even after apparently successful treatment relapse is common. The incidence of such infections in female diabetic patients is much higher than in the general population (Barnard *et al.*, 1953) and, like any infection in the diabetic subject, is apt to complicate the control of their disease. The three diabetic women included in this study were seriously ill on account of urinary infections which had proved resistant to multiple courses of sulphonamide and antibiotic treatment. In contrast, a single course of cycloserine, 250 mg. thrice daily for 14 days, gave a prompt and lasting remission of the infection, with consequent striking improvement both in their general health and in the state of their diabetes. The two

young non-diabetic women had fulminating and very alarming illnesses due to coliform infection of the urinary tract, which was rapidly and completely controlled within 48 hours of starting treatment with cycloserine.

The strains of *E. coli* encountered in the present series have all shown similar sensitivities to cycloserine *in vitro*, though much more resistant strains have been reported by other workers (Hughes *et al.*, 1958). In part at least, this discrepancy may be attributable to differences in technique for determination of minimum inhibitory concentrations. The levels of the drug found in the plasma in the present study are considerably below those required for effective *in vitro* inhibition, and it may be that only as a result of concentration of the drug in the renal tubules is an effective bacteriostatic or bactericidal concentration attained. If this is so, infections due to *E. coli* elsewhere in the body may respond less satisfactorily than those in the urinary tract.

It is noteworthy that the patient (Case 3) whose renal function was most seriously impaired attained urinary sterility more slowly than the others, and this was associated with a slower rise in urinary concentration of the drug and with a much higher plasma level. For these reasons, cautious administration is advised in the presence of established renal damage.

It seems likely that *E. coli* infections of the urinary tract, which do not commonly respond completely to existing chemotherapeutic regimes, will often yield to cycloserine therapy. The results of this small study are, in our opinion, encouraging enough to justify a more extensive trial of cycloserine in a larger series of patients with infection of the urinary tract due to *E. coli* and other coliform organisms. This study is at present proceeding.

Summary

Five patients with severe urinary infection due to *E. coli*, three of whom were diabetic subjects, were treated with cycloserine, 250 mg. thrice daily for 14 days. Complete clinical and bacteriological remission was achieved, without subsequent relapse during a follow-up period of from two to seven months.

Mild toxicity, encountered in one patient with impaired renal function, did not interfere with treatment.

We acknowledge a generous grant from Messrs. Eli Lilly and Co. Ltd. for equipment, and also for supplies of cycloserine. We thank Dr. J. S. Robson and Dr. Mary McDonald for carrying out the renal biopsy studies.

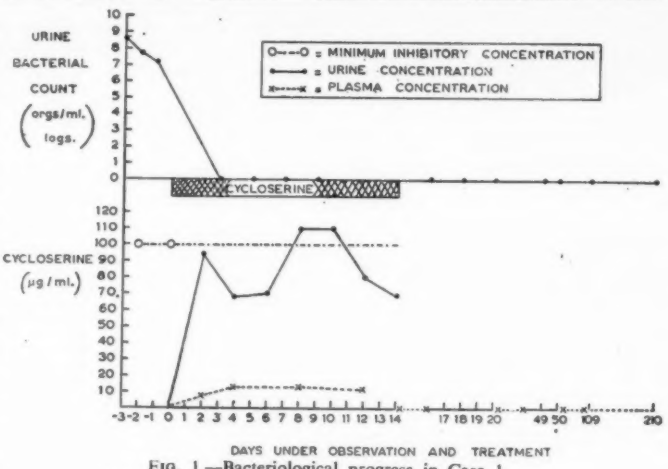

FIG. 1.—Bacteriological progress in Case 1.

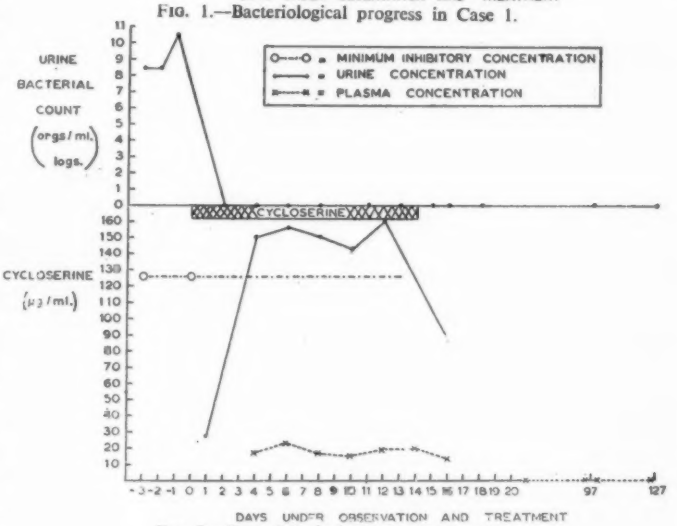

FIG. 2.—Bacteriological progress in Case 2.

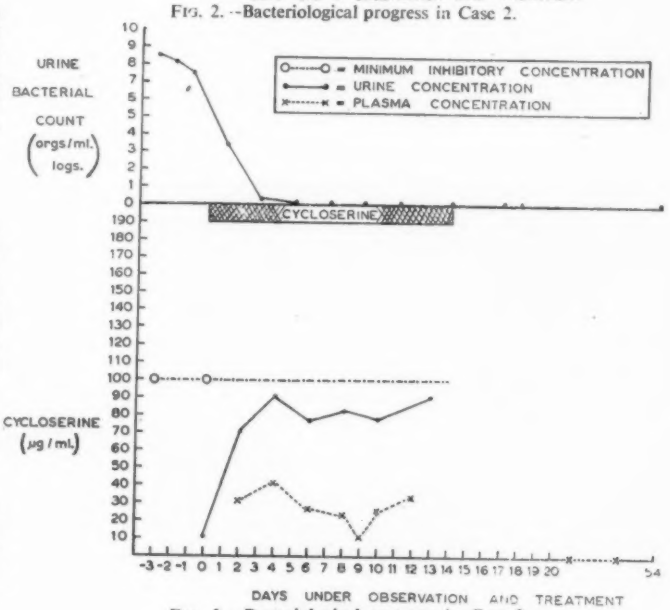

FIG. 3.—Bacteriological progress in Case 3.

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CAESAREAN SECTION SCAR SAFETY

BY

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After a caesarean section, the question "Once or always?" still remains most pertinent, the answer to which verges on gambling. There is no clinical test for the estimation of scar safety in a subsequent pregnancy or labour short of the practical experience. Radiology is capable of providing guidance in some cases.

A recent specimen of a uterus previously subjected to a lower-segment caesarean section and later removed because of fibroids shows quite clearly the typical appearance of a healed transverse incision in the lower segment (Fig. 1). On opening all uteri which have previously been subjected to lower-segment caesarean section a larger or smaller depressed scar will always be seen. That this scar is at the site of the previous caesarean section can be confirmed by inspecting Fig. 2. A hysterogram prior to opening this particular uterus shows a sound in the external scar and the typical internal depression at the same level (Fig. 3). Histopathological evidence (Fig. 4) adds further confirmation in that this thinned area, with both an external and an internal depression, consists entirely of fibrous tissue.

Now this finding, far from being unusual, is present after all lower-segment caesarean sections. Poidevin and Bockner (1958) previously reported the results of a

FIG. 1.—Arrow points to the typically seen scar of a previous lower-segment caesarean section.

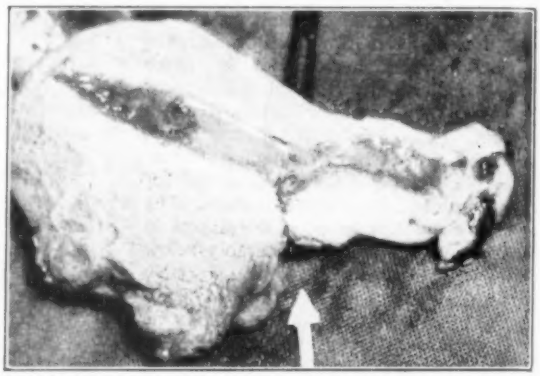

FIG. 2.—Arrow points to the external scar of a previous lower-segment caesarean section shown at the same level as the internal scar.

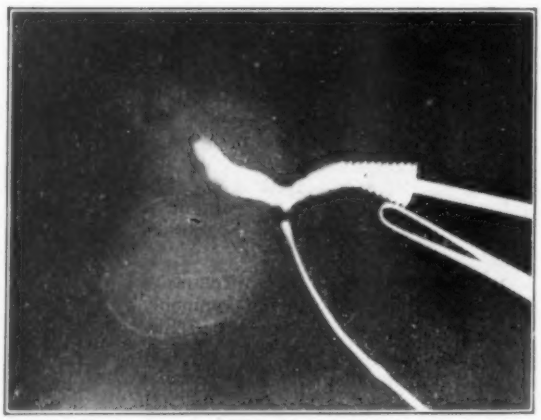

FIG. 3.—Hysterogram of same uterus, as in Fig. 2, before opening. The sound is in the external scar, and the internal scar is shown by a typical wedge-type deformity.

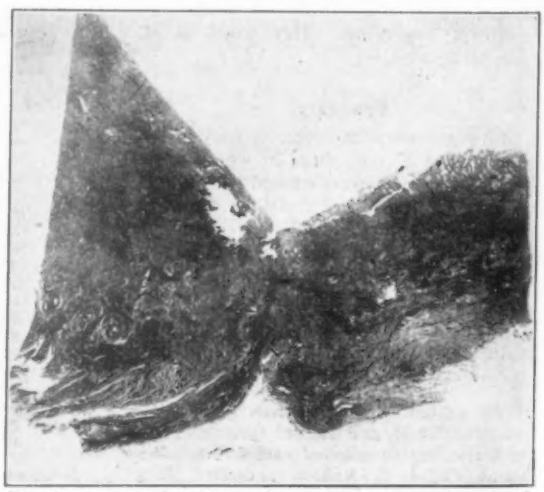

FIG. 4.—Section of scar area from same uterus as in Figs. 2 and 3.

hysterographic study of uteri after caesarean sections and compared the findings between 13 control subjects who had vaginal deliveries and 43 who had caesarean section deliveries. The lateral *x*-ray view was used, and is again stressed because of the position of the lower-segment wound, which would not be expected to show up in an antero-posterior view. All the control cases showed a smooth anterior lower-uterine outline (Fig. 5). All the 43 section cases showed some deformity. The deformities usually took the form of a wedge depression (Fig. 6), but occasionally a larger irregular deficiency was shown (Figs. 7 and 8).

Since this report, further cases have been examined hysterographically by Bockner, and again all previously sectioned uteri showed some deformity. (All figures used here are from the new series.)

The only other reported work on this subject that a previous search revealed was that of Baker (1955). His study concentrated on a digital palpation of the previous section area immediately following subsequent vaginal delivery, and found that 53 out of 64 examined had sound scars. In 24 he carried out hysterograms, but was able to demonstrate a deformity in the lower anterior uterine wall in only five cases.

Significance of the Deformity

It is not permissible to label all these deformities as defects. There is no proof that they are all defective. In fact, there is much proof to the contrary in the abundant clinical evidence of subsequent safe vaginal delivery in many cases. Further investigations and follow-up of our cases tend to confirm the view that the small wedge deformities—that is, those of 5 mm. or less in depth—are those on which reliance can be placed. On many occasions now, at repeat caesarean section in such cases, no deformity has been found in the lower segment except the white scar line. No doubt as the lower segment is stretched out in late pregnancy over the enlarging presenting part this deformity, involving scar tissue, is pulled out and holds quite well.

One of the cases used in the previous report showed an irregular deformity high in the cervix. The patient subsequently passed uneventfully through an easy vaginal delivery, and then in the next labour suffered an extensive rupture from the site of this deformity in the cervix. The details of this case form the subject of another publication at present being prepared by Bockner.

In the search for the real significance of these *x*-ray findings this case seems to emphasize that deformities, other than the acceptable wedge type, are to be distrusted, and in the present state of our knowledge should serve as an indication for repeat caesarean sections. Further, in the irregular deformities the integrity of the scar should be suspect during the whole pregnancy.

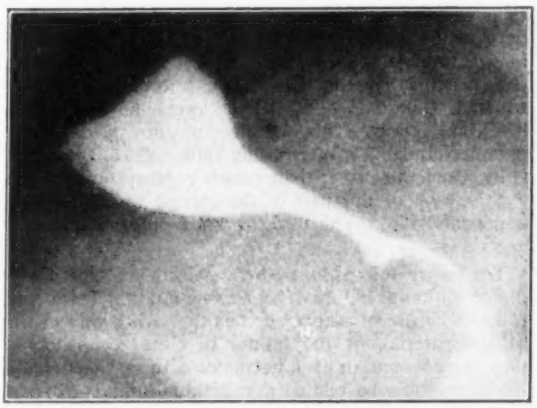

FIG. 6.—Hysterogram nine months after a lower-segment caesarean section. Note wedge-type deformity on lower anterior uterine wall at site of scar. This is a typical finding.

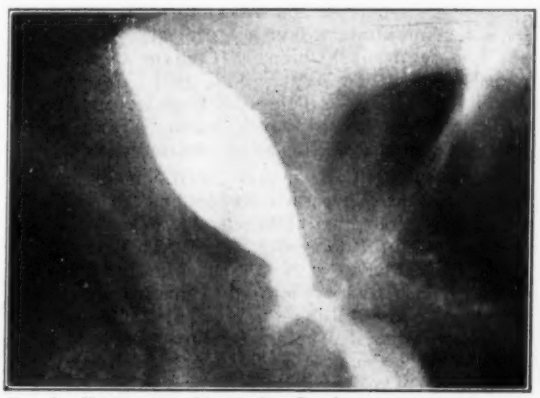

FIG. 7.—Hysterogram 11 months after lower-segment caesarean section. Note irregular deformity at site of scar.

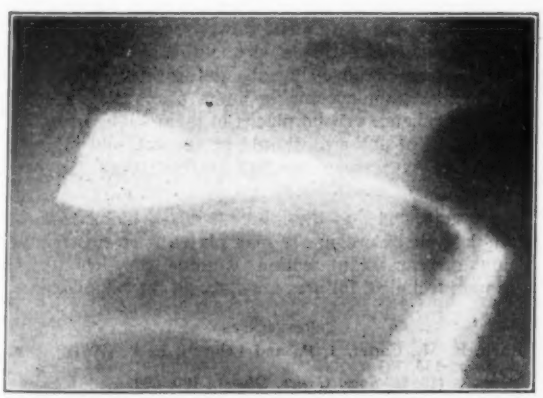

FIG. 5.—Hysterogram six months after a normal vaginal delivery. Note smooth contour of anterior uterine and cervical walls.

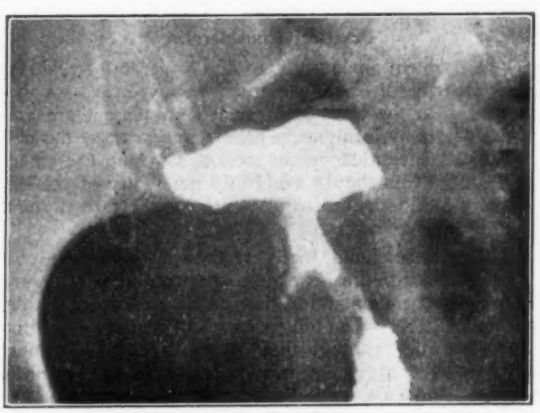

FIG. 8.—Same uterus as in Fig. 7, showing antero-posterior view. This demonstrates a lateral pouching.

Suggested Reasons for the Uterine Deformity

The lower uterine segment is composed of smooth muscle, and this tissue is known to heal by scar-tissue union (Schwarz *et al.*, 1938 ; Siegel, 1952). The original length of the uterine wound is approximately 3 in. (7.5 cm.) at the time of its surgical suture. Within the next few days scar tissue is laid down by fibroblastic activity, while concurrently a gradual and relatively rapid shrinkage of the whole uterus is occurring. Thus the scar tissue which sets out to heal a 3-in. (7.5-cm.) long wound is reduced, after a few weeks, to a $\frac{1}{2}$-in. (1.3-cm.) long wound. This is an extraordinary situation which is found only in such an organ as the rapidly involuting uterus. Thus some redundancy of scar tissue is understandable in the resting state. Also, the union is by scar tissue rather than muscle regeneration, so that a narrowing of this part of the uterine wall (Fig. 4) is understandable. The wedge-shaped deformity is thus explained.

The larger and more irregular defects are most likely due to an initial failure of scar-tissue union. This could follow a technical defect, such as the giving way of the suture material, or the failure to close completely a torn angle wound or even haematoma formation. Could it also possibly be related to a residual inherent hypercortisonism of pregnancy ?

Defective union of wounds, due to a failure of fibroblastic reaction, is well known in such conditions as Cushing's syndrome and during cortisone or corticotrophin administration, both experimentally in animals and therapeutically in humans (Creditor *et al.*, 1950 ; Alrich *et al.*, 1951 ; Baxter *et al.*, 1951 ; Conway and Stark, 1951). In all these conditions we are able to attribute the failure of wound healing directly to the increased amount of circulating corticosteroids.

Pregnancy itself is another condition of marked adrenal cortical hyperactivity leading to increased amounts of circulating corticosteroids (Venning, 1946 ; Gemzell, 1953 ; Robinson *et al.*, 1955 ; Jailer, 1956 ; Gold, 1957 ; McKay *et al.*, 1957). This rise in steroid blood levels persists into the puerperium for a questionable time, Robinson *et al.* (1955) stating that six weeks is required before a return to normal levels is achieved. Could it be that, in some women, this inherent hypercortisonism of pregnancy, which continues into the puerperium, causes a failure of fibroblastic reaction and thus poor healing of caesarean section wounds ?

Practical Considerations

The problem obviously is to find a measure by which the integrity of each caesarean section scar can be judged. In the absence of such a measure there are those who may legitimately believe and practise the old dictum, " Once a caesarean section, always a caesarean section." This should avoid any possibility of uterine rupture in labour, but will not prevent the rare rupture during pregnancy.

On the other hand, there are those who would argue that uterine rupture is so rare after the modern lower-uterine-segment operation that repeat caesarean section is unjustifiable when the original indication does not recur. They support their argument with statistics. This line of argument was suggested in the previous report (Poidevin and Bockner, 1958) when in the preceding five-year period, during 17,000 deliveries, there had not been a case of uterine rupture. Of 216 women who had previous caesarean sections, 83 were selected for subsequent vaginal delivery and safely conducted through, while 133 had repeat sections. Since then there have been two cases of uterine rupture in the clinic service of our teaching hospitals, both having had previous caesarean sections. One was the case referred to previously with the grossly deformed upper cervix on hysterography, the other an emergency admission on whom no hysterography had been done. Thus the statistics have changed from no cases of rupture in 17,000 deliveries to 2 cases in 21,000 deliveries.

There are many reports of scar weaknesses and even scar ruptures found at the time of elective repeat caesarean sections ; conversely, there are many reports of large numbers of cases safely conducted through vaginal deliveries subsequent to caesarean sections. What, therefore, is the correct scientific approach to the individual under one's own care ?

I believe most of us who have been satisfied with the technical details and subsequent post-operative course of the previous caesarean section would trust that wound to a future vaginal delivery. In spite of this faith, however, some large defects have been shown by hysterography in a series of cases that were each the responsibility of a specialist obstetrician.

X-ray evidence has been demonstrated as a means of visualizing the deformity in the uterus after caesarean section. From this an opinion can be given on whether the deformity is within the normal acceptable wedge type range or whether it is an irregular pouching.

We therefore have the alternatives of firstly judging the safety of caesarean section scars after an appraisal of the details of the previous operation and puerperium, or, secondly, of requesting any *x*-ray evidence of scar weakness as judged by an irregular deformity. Reliance on the former has been found insecure on occasion, whilst the small amount of *x*-ray evidence to date suggests that it may be safe to rely on the integrity of the commonly seen wedge deformity but not on large irregular ones. Both methods should be used in cases of doubt even if not practicable in all cases. So often new cases coming under one's care are already pregnant, giving one no opportunity to use hysterography. However, in the non-pregnant state, when evidence of scar safety is sought, hysterography has a definite place.

Conclusion

Hysterography is an advance in our search for evidence of the safety of lower-segment caesarean section scars. Experience strongly suggests that the usually seen wedge-shaped deformities may be considered within acceptable limits of normal healing, and most reliance can be placed in them. The irregular deformities, of any size, should be suspect, and indicate subsequent caesarean section rather than vaginal delivery.

It is suggested that the inherent raised blood corticosteroid levels of pregnancy may play a part in defective union of caesarean section wounds of the uterus, although technical failures must accept the major blame.

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DIABETES INSIPIDUS ASSOCIATED WITH TUBERCULOUS MENINGITIS

BY

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Diabetes insipidus is a rare syndrome of water-balance disturbance characterized by the excretion of excessive quantities of urine with resultant polydipsia.

Apart from heredity, the common causes of diabetes insipidus are trauma, encephalitis, brain tumours (such as gliomata, craniopharyngiomata, meningiomata, or chromophobe adenomata of the pituitary gland), syphilis, Hand–Schüller–Christian disease or xanthoma, and cerebrovascular accidents (Fink, 1926, 1928; Warkany and Mitchell, 1939; Biggart, 1935; Wyllie, 1943; Jones, 1944; Soffer, 1956). Meningitis is an extremely rare cause. In Fink's (1928) series tuberculoma and tuberculous meningitis comprised 5% of cases, with non-syphilitic inflammatory conditions 9%. Soffer (1956), in a review of 160 cases collected from the literature, states that inflammatory diseases (that is, encephalitis, meningitis, tuberculosis, and syphilis) accounted for 31 cases (20%). Jones (1944), observing 42 cases, mentions only one associated with meningitis; and Hagenbach (1883) reported one case of diabetes insipidus resulting from tuberculous meningitis. Healy (1935) gave an account of a case occurring in a child of 2½ years with miliary tuberculosis and basal meningitis. Acheson and Smith (1958) described a case of tuberculous meningitis in which diabetes insipidus occurred five years after the onset of the infection. Lorber (1958) reported a similar association, and briefly reviewed 11 other cases which appeared mainly in the European literature.

In view of the rare association of diabetes insipidus with meningitis, a further case is here presented.

Case Report

A 5-year-old Bantu girl was admitted to the paediatric unit, Coronation Hospital, on October 12, 1956, with the complaint of headache for one month, a painful and stiff neck for three weeks, prominence of the eyes, and thirst and polyuria associated with marked weight loss. There had been no previous illnesses and the family history was non-contributory. The child's developmental history was normal.

Examination revealed a thin, undernourished child lying curled up in bed, very irritable and uncooperative. Stiffness of neck and back was present, and a marked proptosis of both eyes with bilateral sixth-nerve palsies was noted. Fundoscopic examination revealed temporal pallor of both disks. Reflexes were equal but accentuated, and the plantar response was normal on both sides. Tone was normal. The pulse rate was 110, respirations 28, temperature 99° F. (37.2° C.), and blood pressure 100/60 mm. Hg.

The cerebrospinal fluid showed numerous pus cells and lymphocytes, but no bacteria were detected on direct or cultural examination; protein, 230 mg./100 ml.; chloride (as NaCl), 640 mg./100 ml.; sugar, 27 mg./100 ml. The leucocyte count was 11,000/c.mm. Urinalysis was normal. Patch test for tuberculosis was negative (activity equal to 0.0001 ml. (0.1 mg.) of Old Tuberculin). Radiological examination of the heart and skull showed nothing abnormal; the pituitary fossa and sinuses were normal; the lung films showed hilar adenopathy with perifocal pneumonia (Fig. 1). While awaiting the cultural examination of the C.S.F. the patient was treated with soluble penicillin, 250,000 units, and sulphadiazine, 0.5 g. every six hours.

She remained febrile, with temperatures rising to 102° F. (38.9° C.). Polyuria and polydipsia continued, with daily variation in quantity. Re-examination of the C.S.F. showed 60 polymorphonuclears and 45 lymphocytes per c.mm. and protein 1,700 mg./100 ml., with insufficient fluid for sugar and chloride estimations. As the patient's condition had deteriorated, with persistence of the pyrexia, sulphadiazine was stopped on October 19 and tetracycline, 62.5 mg., was given every six hours. Thereafter the proptosis receded and the temperature started to settle. The C.S.F., however, showed no essential change.

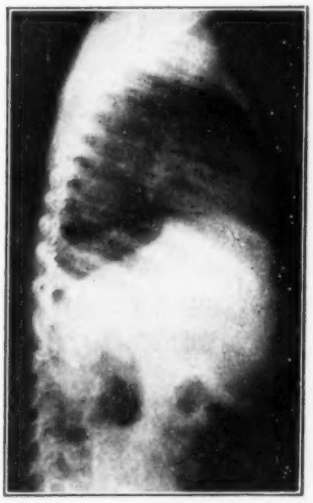

FIG. 1.—Radiograph of chest (right lateral) on October 12, 1956, showing hilar adenopathy and perifocal pneumonia in the right lower lobe.

On November 11 a Mantoux test with purified protein derivative (second strength) was positive and treatment was altered to intramuscular streptomycin sulphate, 0.5 g. daily, and oral isoniazid, 0.1 g. three times daily. Thereafter the child showed steady improvement, with gradual return of the C.S.F. to normal. The bilateral sixth-nerve palsies disappeared, but the polyuria and polydipsia continued. On December 8 the patient became dehydrated and required intravenous fluid therapy. Aqueous "pitressin," 0.25 ml. eight-hourly, was then started with dramatic decrease in her fluid intake and urinary output, which fell to near-normal values. She rapidly began to gain weight. Aqueous pitressin was changed to pitressin tannate in oil, 2.5 units daily, on January 16, 1957. She was finally stabilized on alternating daily doses of 2.5 and 5 units. Pitressin therapy was discontinued on March 6, 1957. The fluid intake and urinary output immediately rose.

Further Investigations

Weight 32¼ lb. (14.6 kg.); height 38 in. (96.5 cm.); span 39 in. (99 cm.); lower segment 18 in. (45.5 cm.), ratio upper to lower segments 1:0.9; head circumference 20 in. (51 cm.); chest circumference 21½ in. (54.5 cm.); abdominal circumference 23½ in. (59.5 cm.). Blood urea, 25 mg./100 ml.; plasma chloride, 103 mEq/l.; CO_2 combining power, 21 mEq/l.; serum calcium, 5 mEq/l.; serum sodium,

133 mEq/l.; serum potassium, 5.3 mEq/l.; plasma cholesterol, 210 mg./100 ml.

Urine: *p*H 7.4, chemically and microscopically normal, maximum concentration 1007; urinary urea content, 240 mg./100 ml.; urinary chloride excretion (as NaCl), 1.7 g./l. (3.57 g. in 24 hours). The urea clearance test gave abnormally low figures on two occasions (24% and 23%). On treatment with pitressin, it rose to 51%. Phenolsulphonphthalein excretion test: total excretion after two hours 47.1%; on treatment 77.9%.

Intravenous pyelograms revealed normal kidneys. Hickey–Hare test (see below): with the infusion of hypertonic saline, the urinary flow increased; it fell sharply when 4 units of aqueous pitressin was given by intramuscular injection. In Fig. 2 the patient's response is contrasted with that of a normal child two years older than she.

In the patient the first infusion of hypertonic saline resulted in *no* significant reduction of urinary flow, and for this test to be negative there should be a reduction of at least 75%. She showed, rather, a rise in urinary flow, which we felt was significant in itself, and this was reduced only with the administration of pitressin. This was in complete contrast to the curve obtained in the normal subject and what was described by Hickey and Hare (1944) and Carter and Robbins (1947). We felt justified, therefore, in accepting this as a positive test.

Pitressin tannate was restarted on March 28, 1957, with the dose on which the patient was previously stabilized. There was again a dramatic reduction in urinary output

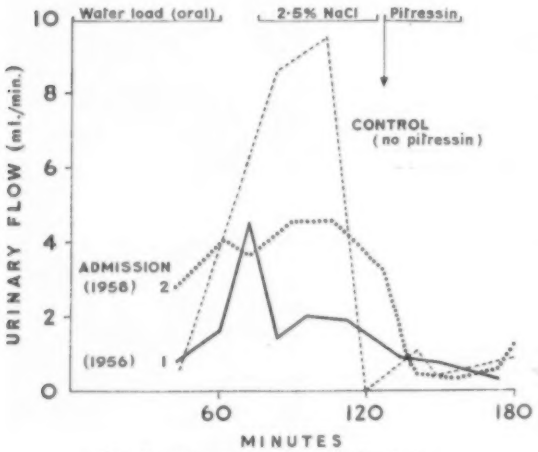

FIG. 2.—Hypertonic saline infusion tests.

and fluid intake. Five days later, however, the dose had to be reduced to 2.5 units daily, as abdominal pain developed and the urinary output had fallen markedly. On the latter dose she was well maintained and had a daily urinary output of 1–1.5 litres. She was discharged from hospital on April 26 to the Margaret Ballinger Home for Bantu Children, still receiving streptomycin and isoniazid.

Progress

Treatment with streptomycin and isoniazid was continued until October. She was then well, but still required pitressin daily to control her urinary output, which had been falling steadily. Pitressin was therefore reduced to 2.5 units on alternate days and subsequently was stopped completely in an effort to wean the child from the hormone. Though the immediate result was promising, she relapsed and was readmitted on March 18, 1958. A full clinical examination was completely normal.

The daily fluid intake and urinary output varied greatly from day to day, the former usually 5–9 litres and the latter 3–6 litres (Fig. 3). Haemoglobin, 16.0 g./100 ml.; P.C.V., 43%; M.C.H.C., 37%; leucocytes, 9,700/ c.mm. Cerebrospinal fluid: 3 lymphocytes/c.mm.; protein, 15 mg./100 ml.; chloride, 569 mg./100 ml.; sugar, 45 mg./100 ml. Serum electrolytes and urinalysis revealed no abnormality. Urine concentration test, 1007 (after 16 hours). Urea clearance test, 81% of average normal renal function (corrected for body size). Phenolsulphonphthalein excretion test, 68.9%

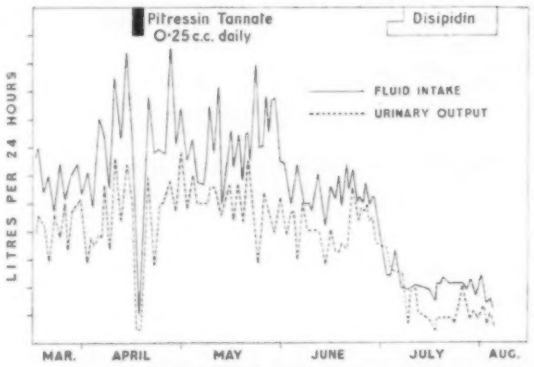

FIG. 3.—Fluid intake and urinary output chart.

excretion (after two hours). The Hickey–Hare test again showed an increased urinary output with the infusion of hypertonic saline solution, showing that the patient was suffering from pitressin-deficient (neurogenic) diabetes insipidus (Fig. 2). F.S.H., 6–12 mouse units/24 hours; 17-ketosteroids, 2.9 mg./24 hours; 17-hydroxycorticoids, 1 mg./24 hours. The glucose-tolerance curve was abnormally low on two occasions, with a fasting level of 70 mg./100 ml.

On April 16 pitressin tannate, 2.5 units daily, was recommenced, and by the following day she had gained 2 lb. (0.9 kg.) in weight but complained of abdominal pain. Two days later she showed signs of water intoxication (headache, nausea, and vomiting, followed by weakness, irritability, and coma); she was incontinent and oliguric. Pitressin was stopped, and in an effort to promote a diuresis 10 ml. of 50% dextrose in water was given intravenously with good effect. By next morning she had improved and was kept under observation for a further period without treatment. In July the use of daily nasal insufflations of pitressin powder (capsules containing 30 units of antidiuretic substance) at 9 a.m. produced an immediate response. The urinary output fell to 2–3 litres daily, but excessive nocturia persisted. The addition of an insufflation at 9 p.m. caused the urinary output to fall to 700–900 ml. daily. She has since been well controlled on this regime, and there have been no untoward effects.

Discussion

As pointed out by Lorber (1958), the site of maximal infection and exudate in tuberculous meningitis is the basal cisterns. The lesion may cause endarteritis and vascular thromboses, with resultant softening and destruction of the surrounding brain tissue, and diabetes insipidus may occur as a result of the anatomical proximity of the pituitary gland and the hypothalamic-hypophysial pathways.

In the observed onset of diabetes insipidus, as in experimental hypophysectomy in animals, or following operative procedures such as the removal of craniopharyngioma, the onset of polyuria and polydipsia is of short duration, lasting approximately five days; an interphase of 10–14 days of normal fluid intake and urinary output follows. This is then replaced by permanent polyuria and polydipsia. The cause of the interphase is not yet fully understood, but two theories have been

postulated. The first suggests that there is a temporary secretion of pitressin by the cells of the median eminence and posterior lobe of the hypophysis, while the second theory states that there is a release of stored anti-diuretic hormone (A.D.H.) from the degenerating posterior lobe. Mudd *et al.* (1957) have shown that sectioning of only the hypothalamic-hypophysial pathway results in diabetes insipidus with interphase, whereas the interphase does not occur if all the vasopressor-secreting tissue is removed—that is, sectioning of the hypothalamic-hypophysial tract with hypophysectomy. Lipsett and Pearson (1956) believe that, at equal solute loads, the severity of the diabetes insipidus depends on the level of stalk section and a preservation of a variable portion of the pars nervosa.

In the case presented here, the symptoms were characteristic: polydipsia was outstanding, as is usual in children. They have been seen to drink water from flower bowls or their own urine to relieve their thirst. Enuresis may occur as the first symptom in children where bladder control has been previously established. In adults the polyuria and the need for fluid may be so great as to interfere with work and sleep. If fluid is withheld in these cases, dehydration rapidly ensues, with headache, fatigue, irritability, muscular pains, weight loss, and tachycardia. Cardiovascular collapse may result. The urine is pale, the specific gravity being between 1001 and 1008 and rarely above 1010. The renal-function tests are usually within normal limits, but the effective plasma clearance may be decreased. This is thought to be due to an impairment in the excretory function of the tubular cells which is restored under the influence of repeated administration of posterior pituitary extract (Winer, 1942). The diagnosis of diabetes insipidus was confirmed by the typical response to standard quantities of hypertonic saline and pitressin. Fig. 2 shows the continued excretion of excessive quantities of urine (failure of the hypophysis to liberate A.D.H.) and the decrease following pituitrin which excludes renal disease (or pitressin-resistant diabetes insipidus). The tuberculous nature of the meningitis was indicated by the active tuberculous focus in the chest, development of tuberculin skin hypersensitivity, and a suggestive cerebrospinal fluid, despite the failure to isolate the mycobacteria. The excellent response to antituberculous therapy, with complete resolution of the meningitis and the subsequent demonstration of calcification in the hilar glands, established this aetiology. The lesion produced by the meningitic process is likely to be situated in the hypothalamic-hypophysial tracts or in the hypothalamic nuclei. It seems unlikely that a lesion occurring in the region of the pituitary gland would produce total destruction of the posterior lobe without affecting the anterior lobe as well. The absence of any signs of hypopituitarism in this patient excludes the latter possibility.

This case exhibits an unusual feature in that the glucose-tolerance test showed a low fasting sugar and an extremely low curve; the usual result is a normal curve or one resembling that of diabetes mellitus. Gibson *et al.* (1927), investigating blood-sugar curves in seven cases of diabetes insipidus, showed persistently increased blood sugars with curves similar to those of diabetes mellitus in six, while only one had an abnormally flattened curve. Bauer (1954), however, in a general survey of hypothalamic disease, found 3 patients out of 10 with flattened curves, and 3 who had a delayed return of the blood sugar to normal. There has been no evidence of malabsorption, and the cause of the flattened curve is not fully understood.

Summary

A case of diabetes insipidus associated with tuberculous meningitis in a child of 5 years is reported. Treatment with nasal insufflation of powdered posterior pituitary extract successfully controlled the patient's polyuria.

My thanks are due to Dr. D. G. Elliot, Medical Superintendent of Coronation Hospital, for permission to publish this report; to Dr. H. C. Falcke, senior paediatrician, and Dr. Harvey Cohen, under whose care the case was admitted, for their constructive criticism; to Dr. J. Meyer for his helpful advice and guidance; and to Mr. A. M. Shevitz, Witwatersrand University Medical School, for the photograph.

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CLINICAL TRIAL OF FURAZOLIDONE IN TREATMENT OF DIARRHOEA

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Medical practice in Bombay is not always comparable with that in the United Kingdom. The standard of living and the conditions under which patients have to be treated are very different from those seen in Western countries. Because of these conditions gastro-enteritis looms large as one of our main therapeutic problems. Another factor is that the continuous advances in the treatment of infectious diseases have produced diverse problems, prominent amongst which is the appearance of extremely virulent pathogenic bacteria which have become resistant to all antibiotics and sulphonamides. The West Bengal Government has warned medical practitioners against uncontrolled or inefficient use of antibiotics, which, if not checked, would increase the incidence of resistant strains of bacteria still further.

Apart from the expense and inconvenience of administering antibiotics and sulphonamides I have found resistant strains develop very readily. This is especially so with *Micrococcus pyogenes* and *Micrococcus aureus. Candida albicans, Pseudomonas aeruginosa, Proteus,* and enterococci are also involved. The necessity for finding a drug which does not produce bacterial resistance and is cheap and easy to administer

has become paramount, particularly in the conditions under which we in India usually have to work.

It is necessary to be aware of the local conditions whenever a clinical trial of a new drug is instituted. Laboratory investigations of stools may be difficult and the follow-up of patients even more so. When, however, a new chemotherapeutic agent which is available for trial appears to be active *in vitro* and *in vivo* against a wide variety of bacteria encountered in intestinal diseases, it must be welcomed and trials begun. The assessment of the results is also a problem, and clinical impressions may sometimes be all that we can offer. In relation to the wide experience we have in the treatment of gastro-intestinal disease a clinical impression may nevertheless be of great assistance in the evaluation of a drug.

A new chemotherapeutic agent, furazolidone ("furoxone"), has been suggested for the treatment of gastro-intestinal infections. It is one of the nitrofurans derivatives, of which group we have previous experience; and the reports of its effects *in vitro* have shown that it is active against a wide variety of organisms. Preliminary clinical trials have already shown that it is effective against, and does not produce resistance in, the organisms commonly encountered in infection of the gut. Furazolidone is bactericidal in low concentrations and has not predisposed to monilial and staphylococcal overgrowth in the faeces. Its effectivity is not apparently inhibited by the presence of mucus, pus, or organic matter, and this is a great advantage in the treatment of enteritis (Yurchenco *et al.*, 1953; Rogers *et al.*, 1956; Ponce de Leon, 1957).

Method and Material

In the latter part of 1958, 58 patients suffering from gastro-intestinal disease were treated with furazolidone. In spite of the difficulties mentioned above, bacteriology of the stool was done in every case. The patients were given tablets each containing 100 mg. of furazolidone, and the usual dose was one tablet four times in 24 hours. No other treatment was given at this time, but the patients were encouraged to drink as much fluid as possible and to eat only if they felt the desire for food. Some of the patients were severely ill, being prostrate and confined to bed. Others were not so ill, and were ambulant while under treatment.

The assessment of improvement was based on the average number of stools on the first day, the average number of stools on the fourth day, and the average number of days for obtaining a complete clinical cure. On occasion it was difficult to obtain accurate figures for the number of stools on the first day of treatment, and the figures shown in this column of the Table must be regarded as approximate and conservative. Figures for the number of stools on the fourth day were certainly accurate. The clinical cure was assessed on the basis that the patients returned to normal work and the number of stools was reduced to that normally passed by each patient before the onset of the infection.

Results

The Table presents the results obtained in the 58 patients investigated. The ages varied considerably, but in almost every case the patient had received 400 mg. of furazolidone each 24 hours. All patients presented in an acute attack, the main complaint being diarrhoea. In 11 patients no growth of pathogenic bacteria was obtained in the stools. All in this group were regarded as clinically cured at the end of four days' treatment. In 47 patients it was possible to obtain pathological evidence of noxious organisms in the stool. Of the 12 suffering from salmonella infections, 11 were cured within four days. In one patient suffering from *Salmonella typhimurium* infection, the stools were still positive, although the patient was clinically cured, after five further days' treatment. In the nine shigella-infected patients, seven were cured at the end of the course of treatment. In two it was still possible to obtain bacterial growth from the stools in the follow-up even after they were clinically cured. In 9 out of 10 patients with *E. coli* growth in the stools clinical cure was obtained in three days; one patient, not cured, still had a positive growth in the stool at the follow-up investigation. Four patients suffering from amoebic dysentery had normal stools within 8 to 12 days of treatment, and *Entamoeba histolytica*, previously present in the stools, was no longer demonstrable. Similarly, seven patients with *Giardia lamblia* in the stools were also clinically cured within four days of treatment and the stools were normal.

Illustrative Cases

Case 1.—A patient 42 years of age had suffered for five days with violent diarrhoea, blood and mucus in the stool, nausea and vomiting, and a temperature of 105° F. (40.6° C.). Haemolytic *Staph. aureus* was grown from the stool. The organism was resistant to tetracycline, chloramphetamine, streptomycin, and penicillin. It was found to be sensitive to furazolidone. This patient was given 150 mg. of furazolidone every four hours for seven days. Within 48 hours the temperature dropped to normal and remained there. Within six days the diarrhoea and all the other symptoms gradually subsided. Follow-up examination of the stool was negative.

Results of Furazolidone Treatment of 58 Patients Suffering from Diarrhoea

Organism in Stool	No. of Patients	Average No. of Stools		Clinical Cure		Failure to Cure No. of Patients	Follow-up Stool Examination	
		1st Day	4th Day	No. of Patients	Average Days		Pathogens Eradicated	Pathogens not Eradicated
Salmonella anatum ..	1	6	2	1	3	—	1	—
" *Derby* ..	4	10	2	4	4	—	4	—
" *Newport* ..	1	7	1	1	3	—	1	—
" *typhimurium*	6	9	2	5	4	1	5	1
Shigella dysenteriae ..	5	12	3	4	5	1	4	1
" *flexneri* ..	3	11	2·5	2	8	1	2	1
" *sonnei*	1	14	3	1	6	—	1	—
Staphylococcus aureus ..	3	9	2	3	4	—	3	—
Streptococcus faecalis ..	2	6	2	2	3	—	2	—
E. coli	10	8·5	3·5	9	3	1	9	1
Entamoeba histolytica ..	4	8	2·5	4	12	—	4	—
Giardia lamblia ..	7	4·5	1·5	7	4	—	7	—
No growth obtained ..	11	8	2	11	4	—	—	—
Total	58			54				

Case 2.—A patient aged 34 was suffering from severe pain in the right side of the thorax, which radiated into the right hypochondrium. *X*-ray examination revealed no pulmonary lesion, but the right dome of the diaphragm was raised and moved imperceptibly with respiration. A diagnosis of subdiaphragmatic disease, most probably amoebic hepatitis, was made, and examination of the stools revealed the presence of *E. histolytica.* After five days' treatment with 400 mg. of furazolidone per 24 hours the chest pain disappeared and the diaphragm was moving almost normally. After a further five days' treatment the patient was very much improved, and no amoebae could be found on repeated examination of the stools. The curative value of furazolidone in this case is certainly not established, and investigations are still in progress.

Discussion

Of a total of 58 patients suffering from diarrhoea due to various causes, 54 were restored to normal within a week of being treated. There is no doubt that some patients may have been cured without chemotherapy, particularly those in whom no growth of pathogenic bacteria could be obtained from the stool before beginning treatment. In my experience the rate of cure for all the patients was most satisfactory and compared favourably with the results previously obtained with antibiotics and sulphonamides.

Twelve patients suffering from salmonella infection responded most promptly to treatment, and within a day or two there was great relief from the muscular aches, fever, diarrhoea, and tenesmus with which this infection is associated. Some of these patients had previously been treated with other measures to which they had not responded. Nine patients with shigella infections were passing characteristic dysenteric stools with mucus and blood when treatment was begun, and a gratifying response was noted within 8 to 10 hours of beginning therapy. Clinically, the patients soon felt very much better, and within 24 hours the stools began to lose their liquid character and developed a more normal colour and consistency. On the average, within three days most patients were subsequently very much better, and once the stools had been reduced to a normal number each day the patients were much improved, but still very weak. It must be stressed that treatment does not cease with the relief of symptoms. Patients require subsequent management with adequate diet and fluids before they are able to return to full employment. This is a common finding with most acute illnesses in my practice, and is certainly due to the normal physical condition of the patients even when no dysenteric infection complicates their living conditions.

It is interesting that seven patients suffering from *G. lamblia* infection responded most satisfactorily to furazolidone after other measures had failed. The four patients suffering from *E. histolytica* infection responded satisfactorily to the treatment, but it is, however, most common to find that in cases of amoebiasis a superimposed infection with a dysentery-producing organism is present. It is clear that furazolidone will readily control the superimposed infections in amoeba-infested patients. Case 2, with the presumed diagnosis of amoebic hepatitis, responded extremely well to furazolidone, as did the other three patients with amoebic colitis. It is far too early to comment on the possibilities of furazolidone in the control of amoebiasis itself, and investigations are being continued. I have no information to offer on sigmoidoscopic examination of the intestinal wall of these four patients, and it is essential that a detailed investigation into this disease should be made.

The side-effects of treatment with furazolidone are said to be nausea and vomiting. It is very difficult to know how serious these may be, because most of my patients presented initially with nausea and vomiting as symptoms of the infection. Only one patient was unable to take the tablets, but none of the others complained of any untoward effects which could be attributed to the drug in question. The results in a group of patients where the pathology is not always simple have encouraged me to continue with this work, and I hope to report later in more detail on certain aspects of what is one of our major problems—amoebiasis.

Summary

58 patients suffering from diarrhoea due to a variety of causes were treated with a new preparation, furazolidone.

The results have shown that furazolidone is a convenient and valuable addition to the drugs available for the treatment of these conditions.

The possibility of the value of furazolidone for the treatment of amoebiasis is being pursued.

I thank Messrs. Smith Kline and French Laboratories Ltd. for the supply of furoxone, and am grateful to Mr. P. Lizioli, of Pharmed Private Ltd., Bombay, for his assistance and co-operation.

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TUBEROUS SCLEROSIS ASSOCIATED WITH SPONTANEOUS HYPOGLYCAEMIA

BY

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Tuberous sclerosis is a rare familial disease of protean manifestations, involving primarily the skin and the nervous system. The characteristic sclerotic patches, to which the disease owes its name, were first described by Bourneville in 1880, and the classical triad of epilepsy, mental retardation, and adenoma sebaceum which characterizes the disorder has been recognized since 1908 (Vogt, 1908). Until then no certain diagnosis had been made in life.

While tuberous sclerosis is often referred to as one of the neuro-cutaneous syndromes, other tissues are often involved. Since the term tuberous sclerosis refers primarily to the changes in the brain, a broader term—"tuberous sclerosis complex" (Moolten, 1942)—is employed to denote the coexistence of tumour-like formations in other organs, notably the skin, heart, kidneys, retina, thyroid, breast, duodenum (Russell

Brain, 1955), large bowel (Budenz, 1950), adrenals (Murphy *et al.*, 1958), bones (Berland, 1953), and lungs (Dawson, 1954).

Though some textbooks (Allen, 1951; Harrison *et al.*, 1958) mention the pancreas among the manifold internal organs involved in this disease, we have found in the literature no reported cases of tuberous sclerosis where the pancreas was affected; the absence of such reports was also stressed by Pagenstecher in his review of the literature on the subject published in 1955.

The following report concerns a case of tuberous sclerosis associated with a secreting adenoma of the pancreas.

Case Report

The patient, an unmarried woman 24 years old, was the second of three children. There was no kinship between her parents; she was born after an uneventful pregnancy and a normal delivery.

At the age of 3 years she had convulsions, not typical for epileptic seizures. Since then the family noticed some degree of mental retardation. Nevertheless the child was enrolled in a regular public school, and not until the age of 9 was she transferred to a school for retarded children, which she left at the age of 12 because she was unable to keep pace with the class. Since early childhood she has loved music, and though she has been unable to learn to read a musical score she plays the piano well, and was pronounced by her teachers to have a sense of absolute pitch.

When she was aged 18, epileptiform seizures appeared, most often in the early morning, between 4 and 6 o'clock. The seizures began with agitation, groaning, and jumping on the bed; then stiffness of the extremities developed and the patient's face grew livid, almost black. A few times involuntary micturition occurred; sometimes she bit her tongue, and once foam appeared on her lips. The most intense seizures occurred during her menses.

At about the same time her father noticed that she sweetened her tea excessively, taking up to six teaspoonfuls of sugar to a cup. She started to sleep very late and would oversleep for hours if not wakened. Eventually the father found that he could wake her by forcing some sweet liquid into her mouth.

The patient was admitted on September 30, 1956, to the Psychiatric Hospital, Talbieh, in Jerusalem, for investigations. On admission she looked her age, behaved strangely, was very agitated, and was anxious to return home. Small reddish-brown spots were noted on her cheeks and chin. All over the body signs of folliculitis were seen. Routine laboratory studies showed no pathological findings, and the neurological examination was normal. A skin biopsy from the face showed a large amount of sebaceous glands. Fasting blood-sugar values were 40–60 mg./100 ml.; the glucose-tolerance curve was as follows: 0 min., 40; 30 min., 104; 60 min., 125; 120 min., 124; 150 min., 90; 180 min., 50 mg./100 ml.

The patient was transferred to Medical Department A of the Hadassah Hospital, Jerusalem, with the diagnosis of tuberous sclerosis, grand mal, and suspected hypoglycaemic crises. The possibility of an insulinoma was raised and a laparotomy suggested, but she had to be discharged a few days after admission because of the Sinai campaign.

During the next two years the frequency of the seizures increased until they became almost daily occurrences; the patient's mental state deteriorated and she put on weight. She was admitted to the Beilinson Hospital on August 26, 1958.

Physical examination showed an obese female with a dull facial expression. Her speech was slow and infantile, and she had no ability for simple arithmetic. Nor did she show any comprehension of her surroundings. Greasy reddish-brown papules, 1–5 mm. in diameter, were scattered in a butterfly pattern over the bridge of the nose and nasolabial folds. Over the breasts and back there were numerous café-au-lait spots.

Laboratory studies showed a normal haemogram. Blood urea was 24 mg./100 ml., and blood cholesterol 205 mg./100 ml. The liver-function tests were normal, and so were the serum electrolytes and proteins. Analysis of urine showed a normal specific gravity, no proteinuria, and no cellular elements or casts. The urinary 11-ketosteroids were 7.2 mg./24 hours and 11-oxysteroids 1.2 mg./24 hours. Ophthalmoscopy showed normal eye grounds, and the electrocardiogram and encephalogram were normal.

Radiographic Studies (Dr. H. Salinger).—The chest radiograph showed clear lung fields. Antero-posterior and lateral views of the skull were normal; there were no signs of erosion of the sella. Pneumoencephalography did not reveal signs of a space-occupying lesion, nor were any abnormalities of the cerebral vessels seen. Examination of

FIG. 1.—Retrograde pyeloscopy of right kidney; side view showing cysts in the renal parenchyma.

the gastro-intestinal tract did not show signs of a pancreatic tumour or of an increase of the mass of the pancreas. Intravenous pyelography showed both kidneys to be of normal size, but the upper and middle calices of the right kidney were elongated and crescent-like, most probably owing to pressure of cysts or expansively growing tumours; the outline of both adrenals appeared normal. This finding was corroborated on retrograde pyeloscopy of the right kidney; a side view (Fig. 1) showed that the cysts were situated ventrally, in the renal parenchyma.

Several biopsies of the skin lesions of the face showed a conspicuous increase of sebaceous glands only. Another biopsy of a facial nodule showed a small subcutaneous tumour (Fig. 2) with large, polyhedral, sharply demarcated clear cells (Fig. 3). This tumour was diagnosed (Dr. J. Casper) as sebaceous adenoma. In another nodular lesion of the face lymphangiectasia was seen.

Studies of the Carbohydrate Metabolism.—During the patient's stay in hospital we witnessed many seizures, which usually occurred around 4 a.m., while she was asleep. She became gradually agitated and started to toss in bed. Her pulse increased to 120/min., but the blood-pressure remained normal—110/70. Clonic movements of the extremities appeared, and passed rapidly into a state of utmost rigidity. A few teaspoonfuls of sweet tea terminated the seizures, and, without waking up, she passed

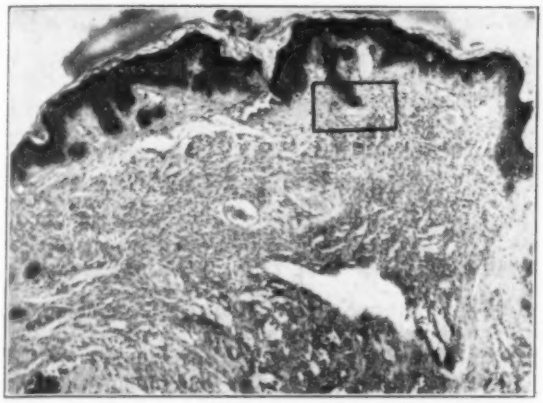

FIG. 2.—Small sebaceous adenoma. (Haematoxylin-eosin. Approx. ×20.)

into a quiet, deep sleep. Repeated blood samples during the seizures showed sugar values of 37–46 mg./100 ml. Fasting of 24 hours invariably released a seizure.

During one of the seizures arterial blood was drawn for estimation of insulin activity of the plasma. The determination (Dr. J. Groen, the Medical School, Jerusalem) was carried out by comparing the effect of the patient's serum, diluted with buffer solution, on the glucose uptake of the isolated rat diaphragm (Groen *et al.*, 1952), with the effect of insulin solutions of known strength on the glucose uptake of the other half of the diaphragm. Her serum had a significantly higher insulin content than 10 milliunits per ml., possibly somewhere between 20 and 50 milliunits per ml. The upper limit for normal ever found was 3 milliunits per ml. (variation of normal 0.1–3.0 milliunits/ml. (Groen *et al.*, 1958)).

Clinical Course.—A laparotomy was performed by Dr. P. Nathan on October 30, 1958, and a round cherry-red tumour, about 3 cm. in diameter, was removed from the body of the pancreas. Palpation of the kidneys disclosed many cysts of various sizes on both sides.

The insulin content of the tumour was determined (Dr. J. Groen), but for technical reasons this was done only after six weeks of refrigeration. The insulin content was found to be 1.6 u./g. of tissue by the ordinary mouse assay method, and 1.0 u./g. by the rat-diaphragm technique. These values are not above those of the insulin content of normal pancreatic tissue (Wrenshall *et al.*, 1952); possibly the insulin content of the tumour may have decreased during the refrigeration period.

Histological examination (Dr. Y. Boss) showed the tumour to be a well-encapsulated islet-cell adenoma of the pancreas, 1.8 × 3 cm. in size, with the typical structure of an incretory organ tumour (Fig. 4), partly with a distinct tubular pattern. No mitoses and no atypical cells were found. Aldehyde fuchsin (Gomori) and chrome alum hematoxylin phloxine (Gomori) stain (Lillie, 1954) showed a relatively small number of cells with fine violet and blue granules respectively, indicating beta cells.

Since the operation (a follow-up of four months) the patient has had no seizures, and supported uneventfully a 36-hour fast, which would have been unthinkable before the operation. The blood-sugar value at the end of the fast was 98 mg./100 ml.

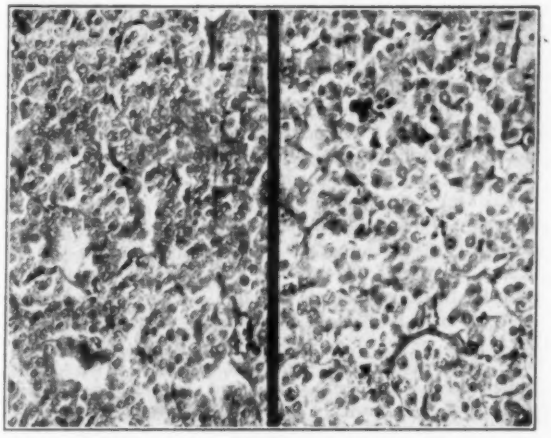

FIG. 4.—Islet-cell adenoma of pancreas: (*a*) typical structure of an incretory organ tumour; (*b*) tubular pattern. (Haematoxylin-eosin. Approx. ×80.)

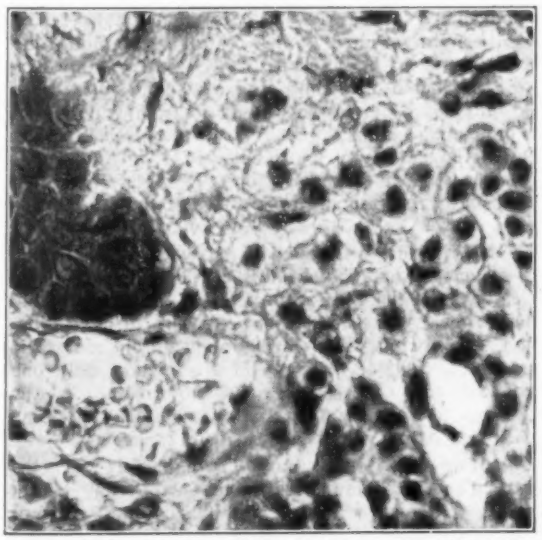

FIG. 3.—High-power view of Fig. 2. The tumour cells of the sebaceous adenoma: large, polyhedral, sharply demarcated clear cells. (Haematoxylin-eosin. Approx. ×190.)

Discussion

The clinical diagnosis of tuberous sclerosis is possible if two or more of the following features can be demonstrated: mental retardation, epilepsy, adenoma sebaceum, phakoma of the retina, multiple mixed tumours of the kidneys, and a familial history of the disease (Moolten, 1942).

The case described showed the following features: mental retardation, grand mal, adenoma sebaceum, and multiple cysts of the kidneys. Therefore it seems to us that the diagnosis of tuberous sclerosis is unquestionable. Tumour-like changes of lymph vessels and blood vessels are known to be associated with tuberous sclerosis (Allen, 1951).

The grand-mal seizures were not of cerebral origin, but proved to be precipitated by spontaneous hypoglycaemia. The elevated serum insulin activity strongly suggested that the hypoglycaemia was due to an insulin-producing tumour of the pancreas (Groen *et al.*, 1952; Vallance-Owen *et al.*, 1955; Willebrands and Groen, 1956). After the excision of the tumour the seizures did not recur during a follow-up period of four months.

The incidence of tuberous sclerosis with mental defect is about one in 300,000 in the general population

(Dawson, 1954), and secreting islet cell tumours of the pancreas are not a common phenomenon. Therefore it would seem that the coexistence of both diseases would not be a mere coincidence. Though this case is, to our knowledge, the first of this kind reported, the possibility may be raised that in a certain number of cases of tuberous sclerosis the "epilepsy" may be caused by an insulin-secreting pancreatic tumour. An appropriate clinical investigation, followed by surgery, may relieve the patients of one of the aggravating symptoms of the disease.

The possibility of involvement of the pancreas in some cases of tuberous sclerosis was raised by Pagenstecher (1955). He reported that an elder brother of a patient with tuberous sclerosis died suddenly at the age of 21 while serving in the Navy. The primary pathological diagnosis at necropsy was acute pancreatic necrosis, and the necropsy report read, in part: "The pancreas is normal in size. It is soft to the point of liquefaction, especially in the body. It is markedly hyperaemic, with hyperaemia not extending past the capsule. Some lobules are preserved. There is no evidence of calculi of the ducts." The author speculates on the possibility that a sudden change in a hypothetical (tubero-sclerotic) lesion, like rupture of a cyst or obstruction of a small duct, could have caused the acute necrosis, while the quick digestion of the tissues by the pancreatic enzymes destroyed all histological traces of the causative mechanism.

It should also be mentioned that van der Hoeve (1933) reported the occurrence of pancreatic cysts in von Recklinghausen's disease, which shows a close relationship to tuberous sclerosis (Lillie, 1954; Wechsler, 1958).

Summary

A case of tuberous sclerosis, marked by frequent epileptiform seizures, associated with spontaneous hypoglycaemia, is described. The patient was operated on and an islet-cell adenoma of the pancreas was removed. Elevated insulin activity in the serum was found. Since the operation the patient has been free from seizures. The possibility of a pancreatic tumour as an aetiological factor of the epileptiform seizures in some cases of tuberous sclerosis is discussed.

We are particularly indebted to Dr. J. Groen, of the Medical School in Jerusalem, for the determination of the insulin content of the serum and the tumour, and to Dr. H. Winnik, of the Psychiatric Hospital Talbieh in Jerusalem, for putting the case records at our disposal. We also wish to express sincere thanks to Mrs. Kaye Norton for producing the illustrations.

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PROCHLORPERAZINE AND IRRADIATION SICKNESS

BY

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A trial is described in which prochlorperazine is compared with pyridoxine and an inert tablet for the relief of side-effects due to therapeutic irradiation.

Prochlorperazine ("stemetil") is a brand of 1-[3-(3 chloro-10-phenothiazinyl)propyl] - 4 - methylpiperazine. This drug is one of the many new anti-emetic preparations now available. It resembles chlorpromazine in its range of pharmacological action, differing, however, in that it is several times more effective as an anti-emetic, but less active in reducing conditioned and instinctive reflex activity and in enhancing the activity of hypnotics and analgesics.

The most distressing side-effects associated with therapeutic irradiation are nausea and vomiting rather than any local reaction at the site of treatment. Anorexia and lassitude may accompany the symptoms of nausea and vomiting, or may occur alone.

Until recently the drug most commonly used in the control of these side-effects was pyridoxine (vitamin B_6), and some authorities have claimed relief of symptoms in a large percentage of cases (Shorvon, 1949; Ellis and Stoll, 1952; Stoll, 1957).

With the advent of a number of anti-emetic drugs having a primarily central action on the "vomiting centre," the suppression of the side-effects of irradiation has become easier.

Stoll (1957) compared a number of these drugs with pyridoxine and discussed their mode of action in the treatment of irradiation sickness. Prochlorperazine was not included in this trial. The use of prochlorperazine has been investigated in the control of vomiting due to a number of unrelated causes (Gray, 1957), and has been compared with chlorpromazine and other drugs in the suppression of artificially induced vomiting in experimental animals (Ducrot and Koetschet, 1956; Boyd, 1957). Ducrot and Koetschet (1956) found that prochlorperazine was four times more effective than chlorpromazine and superior to any of the other drugs used.

As pyridoxine was found to be relatively ineffective in reducing irradiation sickness, a trial series of patients were given 10 mg. of prochlorperazine orally thrice daily before meals prior to the first exposure to irradiation, and were maintained on this dosage throughout their treatment. Of 12 patients on this regime, only one vomited and one developed slight nausea. It was decided to compare the efficacy of prochlorperazine with that of pyridoxine and an inert tablet.

Method.—For uniformity, two tablets of the particular drug were given three times a day before meals. This gave a total daily dose of 30 mg. of prochlorperazine, 60 mg. of pyridoxine, or six inert tablets. The tablets were made up in anonymity, being labelled: A, B, and C; the only person knowing which was which being the pharmacist. Patients were selected

at random, the only discrimination being that those considered unlikely to develop symptoms were excluded. At the onset of nausea or vomiting, tablets A, B, or C, 2 t.d.s., a.c., were prescribed. If after 48 hours there was no relief, in the best interests of the patient prochlorperazine, 10 mg., t.d.s., a.c., was substituted for the unknown tablets. The effect of the tablets on anorexia and lassitude was also noted.

Results

Observations were made of 57 patients who were expected to suffer side-effects from therapeutic irradiation; 12 did not develop symptoms. The results of treating the remaining 45 during the first 48 hours are shown in Table I.

From these figures: $\chi^2 = 12.4$. D.F. $= 4$. $P<0.02$. A probability of this order is significant.

The 20 patients showing only partial or no improvement were changed to prochlorperazine after 48 hours. In 11 cases the symptoms were completely relieved. There was some improvement in five cases, but in the remaining four there was no improvement. Two of these had, of course, already had prochlorperazine. These resistant cases were finally improved by giving a combination of prochlorperazine and chlorpromazine, but in two cases having a marked psychical element phenobarbitone had also to be given.

TABLE I.—*Effect of Prochlorperazine, Pyridoxine, and Inert Tablets on Nausea and Vomiting in 45 Patients Receiving Therapeutic Irradiation*

Drug	No. of Cases	Complete Alleviation	Partial Improvement	No Improvement
A (inert)	15	5	4	6
B (prochlorperazine)	16	14	2	Nil
C (pyridoxine) ..	14	6	5	3

TABLE II.—*Analysis of Effect of Prochlorperazine, Pyridoxine, and Inert Tablets on Alleviating Side-effects of Irradiation, Including Anorexia and Lassitude*

Drug:	B Prochlorperazine	C Pyridoxine	A Inert Tablets
Total No. of cases treated	34	14	15
Cases improved	25 (73·5%)	5 (36%)	6 (40%)
Complete relief of all symptoms	5 (15%)	4 (29%)	2 (13%)
Lassitude present ..	18 (53%)	2 (14%)	2 (13%)
Mild anorexia present ..	14 (41%)	2 (14%)	Nil
Marked anorexia present	6 (18%)	Nil	3 (20%)
Mild nausea present ..	4 (12%)	2 (14%)	2 (13%)

Toxicity

In the dosage used (30 mg. a day) prochlorperazine is remarkably free from toxic effects. In higher doses it may cause slight drowsiness and interference with accommodation (Gray, 1957), and in doses of more than 60 mg. a day confusion, dizziness, and fainting have been reported (Friend and McLemore, 1957). The manufacturers describe more bizarre forms of toxic effects occasionally encountered with very large doses, but none of these occurred in the trial described.

In this series it is difficult to evaluate whether any drowsiness encountered was due to the drug used or to the effects of irradiation. Apart from the occurrence of slight drowsiness in a small number of cases, there was no evidence of any undesirable constitutional side-effects in any of the patients treated.

Regular blood examinations showed no appreciable change in the cell count that could not be attributed to irradiation except in one case. This was a female patient aged 72 receiving post-operative irradiation following a local mastectomy for carcinoma of the breast. The total white-cell count dropped to 1,200 after one week of irradiation and treatment with prochlorperazine. After about two weeks at this level there was a gradual return to normal, in spite of continuing both the irradiation and the prochlorperazine.

No other toxic effects were encountered.

Summary and Conclusions

In a controlled trial involving 45 patients receiving therapeutic irradiation, prochlorperazine has been found significantly more effective in relieving radiation sickness than pyridoxine or inert tablets.

The following conclusions may be drawn from the small series described: (1) Prochlorperazine is more effective in relieving the toxic symptoms of irradiation than pyridoxine or an inert tablet. (2) In the dosage of prochlorperazine used (10 mg. t.d.s.) there were no material side-effects; marked drowsiness as occurs with so many other anti-emetic drugs was not seen. (3) For maximum benefit it is best to begin giving prochlorperazine with the first exposure to irradiation, or at least as soon as possible after the onset of symptoms.

I thank Dr. I. Churchill Davidson for allowing me to conduct this trial on his patients and for his helpful suggestions and criticisms.

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Preliminary Communications

"Debricin": A New Agent for Wound Debridement

The presence of necrotic tissue in an open wound is an obstacle to healing. Infection persists, granulations are slow to appear, and epithelization is delayed. For small and superficial sloughs, routine treatment with local antiseptics and rest for the affected part usually provide sufficient help for the natural reparative processes to allow healing to occur within a reasonably short period of time. When a slough is of greater extent in depth or size, healing by this means is slow and may extend over many weeks, and it may also prevent the early application of a skin graft in suitable cases. For this reason, surgical excision of deep and extensive sloughs is often preferred, and may be combined with immediate skin-grafting.

Another way of tackling this problem is to rely on one of a variety of enzymatic preparations, application of which accelerates the removal of necrotic tissue and sloughs, which are broken up by proteolytic digestion; thus the period of healing or of wound preparation prior to a plastic procedure is greatly shortened. This approach has been investigated by others. Morani (1953) reported great improvement in six cases of chronic sloughing lesions using a trypsin preparation. A mixture of trypsin and chymotrypsin was used by Reiser, Roettig, and Curtis (1953), who found very rapid clearance of sloughs in similar lesions. Prueter, Stein,

Drum, and Kalz (1957) applied a preparation of chymotrypsin only and reported excellent response in 75% of a series of 60 patients.

Shelby, Taylor, Garnes, and Prigot (1958) used "viokase," a preparation of whole pancreatic extract, with similar success on 125 patients. Spittler and Parmenter (1954) reported their general impression of the use of a mixture of streptokinase and streptodornase on sloughing war wounds, and were also greatly impressed by the rapidity of slough clearance with these agents. "Debricin" was used by Douglas, Ferriday, and Gaughran (1958) in an experimental study on removal of necrotic tissue in guinea-pigs subjected to a standardized type of burn and found it greatly superior to five other enzyme preparations of similar nature.

Present Trial

A short trial of debricin was therefore organized to assess its value in relation to the rapidity of disappearance of necrotic tissue and sloughs in suitable patients. Debricin is a protease extracted from fig latex and presented as a lyophilized (freeze-dried) powder, containing the active ingredient, which immediately before use is dissolved in a vegetable gum with suitable preservatives and buffers. This fig protease is a highly specific lytic agent with a pronounced effect on fibrin, denatured elastin, and denatured collagen, but no effect upon living or even partially denatured tissues. It is available in two strengths—1% and 7.5%.

During the period of the trial, all in- and out-patients whose lesions were of a suitable nature were included, irrespective of whether previous treatment had been given. All sites were included, and the pathology of the lesions ranged from traumatic necrosis to chronic ulceration. Size, aetiology, and total duration of each lesion were recorded to provide the clinical background to the individual case. Previous treatment consisted most frequently of various combinations of commonly used antibiotics, local applications of eusol, and similar antiseptic solutions, and supporting bandages and rest for the affected part. Infection of the whole lesion was estimated in the general clinical sense of this term and was divided into three degrees of severity. Two types of slough were recognized: partial-thickness skin necrosis (group A), and full-thickness skin necrosis with or without additional necrosis of the superficial layers of the subcutaneous tissues (group B). The duration of the sloughs is stated separately, as in some cases these were of more recent occurrence than the primary lesion. Treatment consisted in the application of debricin directly to the slough, the whole wound then being covered with a simple dry gauze dressing.

In order to present suitable control cases, it would have been necessary to provide for each debricin-treated case one of similar aetiology, duration, size, and depth to be treated with standard methods only. Perusal of the tables of treated patients shows that among the entire series it would have been difficult to find similar cases for this purpose. Therefore as adequate controls could not be obtained they were omitted, and assessment of the results was made on the extent of clearance of slough after five days' treatment. Where treatment continued for longer, the time factor was also taken into consideration.

TABLE I.—*Lesion*

Sites		Duration		Pathology	
Arm	3	0–7 days	5	Abrasions	9
Hand	1	8–14 ,,	4	Ischaemic necrosis	5
Finger	1	15–30 ,,	4	Stasis ulcer	15
Leg	26	30+ ,,	20	Infection	3
Face	1			Irradiation necrosis	1
Chest wall	1				

Previous Treatment		Infection		Size	
Antibiotics	13	Heavy	11	<1 sq. in. (6·45 cm.²)	9
Local antiseptics	19	Moderate	15	<4 ,, (25 ,,)	11
Bandage/rest	23	Slight	7	<9 ,, (58 ,,)	5
				>9 ,, (58 ,,)	7
				Not known	1

Figures in all three tables indicate number of cases.

TABLE II.—*Slough*

Type		Duration		Size	
Group A	5	0–7 days	7	<1 sq. in. (6·45 cm.²)	13
,, B	28	8–14 ,,	8	>1 ,, (6·45 ,,)	12
		15–30 ,,	2	>4 ,, (25 ,,)	8
		30+ ,,	13		
		Not known	3		

TABLE III.—*Treatment and Results*

Treatment		Duration		Additional Treatment	
Debricin 1%	22	0–7 days	27	Antibiotics	1
,, 7·5%	11	8 days+	6	Local antiseptics	2
				Bandage/rest	24

Results		Adverse Reactions	
Good	18	Slight pain	7
Moderate	8	Severe ,,	1
Poor	7	Pain and itching	1

Results

Tables I–III summarize the case details and results, the latter being graded as follows: Poor = little or no effect after five days' treatment. Moderate = 50% or less slough clearance after five days' treatment. Good = 75% or more slough clearance after five days' treatment.

Thirty-three lesions were treated in a total of 31 patients. Though the criterion for assessment of the usefulness of debricin was taken to be the percentage of slough clearance after five days of daily applications, the treatment period is actually longer in those out-patients who were seen only at intervals of several days. The results in these cases have therefore been judged on the total number of applications of debricin required to remove the necrotic tissue, as the total time of treatment was not the deciding factor. There were therefore 18 good results, eight moderate results, and seven poor results. However, in two of the last group treatment was discontinued after one application of debricin owing to the rather severe local discomfort.

Adverse Reactions.—Only local pain was complained of, and no generalized reactions occurred. The former could not be correlated with the degree of inflammation present, or any other local or general factor. In only two cases was it severe enough to stop further treatment, the remaining patients often stating spontaneously at the end of treatment that their discomfort had been negligible in comparison with the satisfactory result achieved. In no case was there any evidence that debricin had any adverse effect on healing.

Summary and Conclusions

Thirty-three open wounds and ulcers were treated with debricin to help with the rapid removal of sloughs and necrotic tissue. The disappearance of necrotic tissue from this type of lesion without the use of such an enzyme preparation is usually slow and delays healing. The best results in this trial were obtained on sloughs which, by the nature of the lesion, were moist and soggy when treatment was begun. Conversely, dry

and leathery sloughs were most resistant to digestion with debricin. In one case the continued presence of pus may have been the reason for the poor result. On the basis of this series of cases, debricin is a valuable adjunct to the standard methods of treatment of this type of lesion both in hospital and in out-patient practice. In successful cases removal of necrotic tissue and healing are greatly accelerated.

We thank the nurses of St. Mary's Hospital, who carried out the treatment of these patients, and Messrs. Johnson & Johnson for providing the debricin.

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Medical Memoranda

Prophylactic Ergometrine

It has been established that the prophylactic use of ergometrine in the second stage of labour reduces the incidence of post-partum haemorrhage (Lewis, 1956): but a recent letter to this *Journal* suggests that many still believe ergometrine used in this way inevitably results in an increased rate of manual removal of the placenta. This belief appears to persist in spite of a number of reports to the contrary (Davis and Boynton, 1942; Shaw, 1949; Kimbell, 1954). The series of cases here recorded adds to the weight of evidence in favour of the prophylactic use of ergometrine.

Table I shows the incidence of post-partum haemorrhage and the manual removal rate at Perivale Maternity Hospital from 1954 to 1957. There was a

TABLE I.—*Incidence of Post-partum Haemorrhage and Manual Removal Rate*

	1954	1955	1956	1957
No. of deliveries	1,010	1,123	1,190	1,292
Post-partum haemorrhage:				
No. of cases	75	80	51	49
Rate	7·4%	7·1%	4·3%	3·9%
Manual removal of placenta:				
No. of cases	14	21	19	14
Rate	1·3%	2·1%	1·6%	1·1%

noticeable decrease in the incidence of post-partum haemorrhage in 1956 and 1957 compared with the preceding years, without any alteration in the rate of manual removal of the placenta. Since 1951 0.5 mg. of ergometrine has been given intravenously with the birth of the anterior shoulder to patients predisposed to post-partum haemorrhage—namely, patients with a history of post-partum haemorrhage, those with a haemoglobin of less than 10.4 g./100 ml. at the onset of labour, patients expecting the fifth or subsequent baby, those with hydramnios or multiple pregnancy, after an ante-partum haemorrhage or prolonged labour, and if operative intervention had been necessary. From the beginning of 1956 all patients not so treated, and delivered in alternate weeks, were given 0.5 mg. of ergometrine together with 1,000 units of hyaluronidase intramuscularly with the crowning of the head. The remainder of the patients were not given ergometrine unless undue bleeding occurred either before or after delivery of the placenta. The results are shown in Table II. The difference in incidence of post-partum

TABLE II.—*Results of Treatment*

	1956	1957	Total	Incidence
No. of deliveries	1,190	1,292	2,482	
No. of post-partum haemorrhages	51	49	100	4%
No. of manual removals	19	14	33	1·3%
Ergometrine given in the 2nd stage:				
No. of cases	464	590	1,054	
P.P.H.	9	16	25	2·4%
Man. Rem.	9	8	17	1·6%
No ergometrine until after delivery of the baby:				
No. of cases	726	702	1,420	
P.P.H.	42	33	75	5·3%
Man. Rem.	10	6	16	1·1%

haemorrhage in the two-year periods 1954–5 and 1956–7 is statistically significant ($P<0.001$). The difference between the number of post-partum haemorrhages occurring in patients treated either with or without ergometrine in 1956 and 1957 is also statistically significant ($P<0.001$). These figures are in fact of greater significance, since the group of patients treated with ergometrine includes those predisposed to post-partum haemorrhage. Further, the patients who were not given ergometrine during the second stage were given it before the delivery of the placenta if the amount or rate of blood loss caused concern. The manual removal rate is almost identical in all four years (P 0.8–0.7).

The series shows that there is no increase in the manual removal rate if ergometrine is used prophylactically in the second stage of labour; and these figures confirm the work of Lister (1950), Daley (1951), and Kimbell (1954). To save blood is of prime importance, and the prophylactic use of ergometrine, particularly in patients who are prone to have a post-partum haemorrhage, certainly does this, as well as shortening the duration of the third stage of labour (Shaw, 1949) without increasing the hazards to the mother.

It is agreed that occasionally, when ergometrine has been given during the second stage, the placenta and membranes may be trapped by the closing cervix; but by practising the Brandt-Andrews manœuvre, if necessary supplemented by the inhalation of amyl nitrite, cervical spasm can be overcome and the separated placenta delivered from the cervix or vagina.

Since these results have become available, ergometrine is being used routinely in the second stage of labour for all patients delivered in Perivale Maternity Hospital.

I would like to thank Miss A. M. Dickins for permission to publish these figures.

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Reviews

COLOUR VISION

Visual Problems of Colour. A Symposium held at the National Physical Laboratory on 23, 24, 25 September, 1957. 2 Volumes. National Physical Laboratory Symposium No. 8. (Pp. 749; illustrated. 42s.) London: H.M. Stationery Office. 1958.

Of the eight reported symposia sponsored by the staff of the National Physical Laboratory, that held in the autumn of 1957 on colour vision, the report of which has recently been published, must rank as one of the most interesting and useful. The proceedings were opened by the Selig Hecht Memorial Lecture by George Wald, of Harvard University, on retinal chemistry and the physiology of vision; then followed 40 papers, all adequately discussed by workers from Great Britain, the U.S.A., Canada, France, Holland, Germany, Spain, Italy, Finland, Sweden, Denmark, Switzerland, Russia, and Japan. A more representative and authoritative company could not have been selected. The various aspects of the subject were considered as follows: visual pigments, particularly in relation to colour vision; brightness-matching and colour-matching; subjective colour measurement and defective colour vision; the electrophysiology of visual stimulation; and theories of colour vision.

Colour vision has attracted much experimental work and more speculation; nevertheless to-day the major problems are still not solved, nor is it likely that they will be until more fundamental work is done on objective methods of inquiry such as photochemistry and electrophysiology of the visual process. Presumably the mechanism functions at three levels—peripherally in the retina, in the transmission line with its possibilities of amplification and modification of the stimulus signalled from the retinal receptors, and in the receptive area of the cortex.

The reader of these two fascinating volumes may well be left with a feeling of frustration because so little can yet be accepted as proven fact; but he will at least be delighted to appreciate how investigators throughout the world are attacking a problem of major importance, from chemical, physiological, and psychological standpoints, not only because of its intrinsic interest, but because its solution promises to throw much light upon the workings of the central nervous system.

STEWART DUKE-ELDER.

ENZYMES

Clinical Enzymology. Edited by Gustav J. Martin, Sc.D. (Pp. 241+vii; illustrated. 42s.) London: J. and A. Churchill, Ltd. 1958.

The object of this volume as described in the editor's preface is to outline the basic knowledge essential to an understanding of the "true structure of the new world of clinical enzymology," but closer reading makes it hard to see the real purpose of this book unless it is to promote the use of enzyme preparations as drugs. It cannot be recommended as an elementary introduction to enzymology, and anyone considering employing enzymic methods in clinical practice would be better advised to turn first to standard textbooks of clinical biochemistry and then to comprehensive reference books in enzymology. But there are some useful chapters in the volume—for example, that by G. V. Rossi, which reviews enzymes whose use has been advocated in diagnosis; and the chapter by M. J. Sullivan, which has some shrewd comments, though the text itself, which deals with the physical chemistry of enzymes, is difficult for the uninitiated.

In the final chapter, on recapitulation and perspectives, it is stated that clinical enzymology is initially dedicated to the control of the macromolecular state, to the proper orientation of secondary valence states, and that it is secondarily dedicated to the proposition that restoration of normal enzymic *milieu* is essential to a return to health, and that a significant directional force toward that restoration can be achieved by the administration of enzymes. This natural philosophy is rather naive, and there is frequently no proof that the administration of non-enzymic protein preparations might not have induced comparable effects. Into this category would fall the observation: "Other traumatic states such as sprains, bruises, traumatic arthritis, cerebral concussions, crush injuries, and fractures respond to therapy. All surgical procedures must by their very nature cause trauma, and in this area enzyme therapy has been firmly established." At the risk of being a "reactionary" the reviewer would want to see more satisfying evidence following a more critical approach.

D. P. CUTHBERTSON.

HEAVY GOING

Basic Surgery. Edited by Leslie Oliver, M.B., B.S.(Lond.), F.R.C.S.(Eng.), F.A.C.S. (Pp. 1,359+xii; illustrated. £6 6s.) London: H. K. Lewis and Co., Ltd. 1958.

By any standards this is a formidable addition to surgical literature. It is large, heavy, and unwieldy; it consists of no fewer than 1,300 pages; and it is expensive. The expressed intention of the editor and his associates was to produce a book for undergraduates; and from its ambitious title the reader could well expect an account of surgical fundamentals. Unhappily, he will be disappointed. The content is wide, the sections are often scholarly and attractive, but what most surgical teachers regard as "basic" surgery is almost completely ignored.

The arrangement of the several parts is not readily comprehensible. The opening chapter treats of appendicitis, and is followed by one on abdominal surgery, where consideration of amoebiasis precedes that of hernia, and cancer of the stomach is dealt with before peptic ulcer. The section that follows is devoted to paediatric surgery, though little attention is paid to the principles that order the paediatric surgeon's approach. Thereafter an excellent account of neurosurgery precedes the chapters on the surgery of the face and lip and neck. But not only is the chapter sequence unusual: the layout of the individual chapters is far from uniform; some are frankly of essay type, and make interesting reading for the expert but a difficult proposition for the undergraduate, who generally benefits from a more systematized approach. The book is weakest in the parts that deal with basic surgery—the care of wounds, the management of severe trauma, respiratory insufficiency, and other complications of operation and accident. The text is profusely illustrated, but the standard of reproduction is variable, and many of the black-and-white photographs of surgical specimens are quite unhelpful. More liberal use of line drawings, especially in the section on fractures, would have increased its usefulness.

These criticisms are not meant to imply that the book is without virtue. In fact, as contributions to surgical

literature most of the chapters are good. But the book as a whole must be judged against its declared purpose. The undergraduate of to-day has already a bewildering assortment of surgical textbooks from both sides of the Atlantic to choose from, each with some particular quality of content or size, though possibly none perfect enough to meet all the demands and escape all the criticisms of both student and teacher. The present book does not supply the perfect answer, and as a students' treatise on surgery it will not displace in value or in appeal either the old favourites or the more recent additions to the undergraduate library.

JOHN BRUCE.

SURGERY OF THE ISCHIUM

Injuries and Surgical Diseases of the Ischium. By Henry Milch, M.D. (Pp. 163+x; illustrated. 84s.) New York: Paul B. Hoeber, Inc. London: Pitman Medical Publishing Co. Ltd. 1958.

It may be thought that a monograph on the surgery of the ischium is unlikely to reveal information that is unobtainable in textbooks. However, there is a place for such a book, as the tendency for students and postgraduates is to think about the pelvis as a whole and fail to focus, when need exists, on the diseases and injuries of this bone. The author has not restricted his text to conditions of the ischium, but has included surrounding soft parts and to some extent neighbouring bones—possibly appreciating that Homer used the word to describe the hip-joint.

The arrangement of the chapters follows textbook pattern—anatomy, and physical and *x*-ray examination, conditions recognized in childhood being placed before injuries and diseases. The remarks on ischium varum and Otto's pelvis are of some interest. Useful descriptions are given of fractures and separation of the apophysis of the tuberosity. Infection of the ischium and its origin are considered, and one chapter is devoted to tuberculosis. There is a brief account of tumours of the bone, and the book ends with diagrammatic and informative matter on surgical approach. There is nothing controversial in the monograph and it is a useful reference book. The reproduction of a number of radiographs is not very satisfactory, the letterpress is excellent, but the price not modest.

ST. J. D. BUXTON.

ORIGIN OF LIFE

The Dawn of Life. By J. H. Rush. (Pp. 258. 15s.) London: English Universities Press, Ltd. 1958.

The purpose of this book, by an American physicist now in consultant practice, seems to be to describe for the general reader what is the present scientific picture of the origin of the earth and of life upon it. Ideas are best communicated when the author or speaker has formed a clear and true picture of his readers or hearers, so that he can select rigorously the material most suitable for them, and reject whatever is not wholly relevant to his main theme or is too difficult of explanation in the particular circumstances. Unfortunately the present author oscillates between labouring the well known and the obvious, and throwing in biochemical formulae and such physical concepts as "resonance" without explanation or purpose. He has written his book in a series of short sections, without making clear his plan or argument, and in a style which is certainly not alive with interest. There are no pictures. The dust jacket is good.

J. L. CRAMMER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Hörtraining. Beschichte, Voraussetzungen, Methodik und Aussichten bei Kindern und Erwachsenen. By Dr. Gerd Beckmann and Dr. Anton Schilling. (Pp. 123+x; illustrated. DM. 24.) Stuttgart: Georg Thieme Verlag. 1959.

Migration et Maladie Mentale. By Yves Champion. Preface by Henri Laugier. (Pp. 110+xi; illustrated. 1,200 fr.) Paris: Librairie Arnette. 1958.

David Livingstone. Family Letters 1841-1856. Volume I 1841–1848, Volume II 1849–1856. Edited with an Introduction by I. Schapera. (Pp. Vol. I: 253; Vol. II: 320. 60s. the set.) London: Chatto and Windus. 1959.

Low Intensity Radium Therapy. By Charles L. Martin, E.E., M.D., F.A.C.R., and James A. Martin, M.D., F.A.C.R. (Pp. 257+xi; illustrated. 90s.) London: J. and A. Churchill Ltd. 1959.

Mechanisms of Hypersensitivity. Henry Ford Hospital International Symposium. Edited by Joseph H. Shaffer, M.D., Gerald A. LoGrippo, M.D., and Merrill W. Chase, Ph.D. (Pp. 754+xx; illustrated. £6 10s.) London: J. and A. Churchill Ltd. 1959.

Dr. Jenner of Berkeley. By Dorothy Fisk. (Pp. 288+vii; illustrated. 25s.) London, Melbourne, Toronto: Heinemann. 1959.

Elementi di Igiene Orale. Norme di Profilassi delle Malattie della Bocca e dei Denti nel Bambino, nell'Adulto e in Particolari Categorie di Lavoratori. By Professor Ornella Santoro. (Pp. 59; illustrated. L. 600.) Rome: Istituto di Medicina Sociale. 1959.

Basic Anatomy and Physiology. By H. G. Q. Rowett, M.A. (Pp. 124; illustrated. 21s.) London: John Murray. 1959.

Disorders of the Temporomandibular Joint. Diagnosis, Management, Relation to Occlusion of Teeth. By Laszlo Schwartz, D.D.S., and 18 contributors. Illustrated by Robert J. Demarest. (Pp. 471+xxiii. £5 5s.) Philadelphia and London: W. B. Saunders Company. 1959.

Clinical Auscultation of the Heart. By Samuel A. Levine, M.D., Sc.D.(Hon.), F.A.C.P., and W. Proctor Harvey, M.D. Second edition. (Pp. 657+xiv; illustrated. 77s.) Philadelphia and London: W. B. Saunders Company. 1959.

Cancer in Families. A Study of the Relatives of 200 Breast Cancer Probands. By Douglas P. Murphy, M.D., and Helen Abbey, Sc.D. (Pp. 76+x. 20s.) Cambridge, Mass.: Harvard University Press (Commonwealth Fund). London: Oxford University Press. 1959.

Family Doctor and Family Problems. By K. F. M. Pole, L.R.C.P., L.R.C.S.(Ed.), L.R.F.P.S.(Glasgow), M.D.(Vienna). (Pp. 111+xi. 10s. 6d.) London: Bloomsbury Publishing Co., Ltd. 1959.

British Medical Bulletin. Volume 15, No. 3. ***Current Virus Research.*** (Pp. 175–250+xvi; illustrated. 20s.) London: Medical Department, British Council. 1959.

An Introduction to Public Health. By Harry S. Mustard, M.D., LL.D., and Ernest L. Stebbins, M.D. Fourth edition. (Pp. 338+xi. 31s. 6d.) New York and London: The Macmillan Company. 1959.

Neurological Complications of Lymphomas and Leukemias. By Henry M. Williams, M.D., Henry D. Diamond, M.D., F.A.C.P., Lloyd F. Craver, M.D., F.A.C.P., and Herbert Parsons, M.D. (Pp. 134+viii. 43s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Resuscitation of the Unconscious Victim. A Manual for Rescue Breathing. By Peter Safar, M.D., and Martin C. McMahon. Illustrated by Colin E. Thompson, Jr. (Pp. 79+xi. 12s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Die Cerebrale Gefäss-Sklerose. Diagnose, Behandlung und Soziale Aspekte. By Dr. Hans E. Kehrer. (Pp. 238+viii; illustrated. DM. 28.) Stuttgart: Georg Thieme Verlag. 1959.

Mitral Valvulotomy. By Harold J. Stewart, M.D., and Frank Glenn, M.D. (Pp. 244+xv; illustrated. 80s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Recent Progress in Oxytocin Research. By B. Berde, M.D. (Pp. 110+ix; illustrated. 36s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

BRITISH MEDICAL JOURNAL
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CHROMOSOMES OF MAN

Recent work on the chromosomes in human cells has added greatly to our basic knowledge of certain clinical conditions, including mongolism and the rarer congenital abnormalities known as Klinefelter's and Turner's syndromes. A report of the symposium held at King's College Hospital Medical School in September is published at p. 1089 this week.

The story has a prelude composed of two parts. Ten years ago M. L. Barr and E. G. Bertram,[1] "with no more elaborate equipment than a compound microscope," showed that the resting nerve cell of female cats had a nucleolar satellite which stained readily with basic dyes, whereas no such body could be detected in cells from males. At the same time the authors reported a similar sex difference in the human subject. These observations have been consistently confirmed in man and experimental animals. The explanation is that in the female the two X chromosomes have more chromatin (and are therefore more visible when stained) than the XY pair in the male. As P. E. Polani[2] has pointed out, the nuclear sexing of Barr is not a complete index of sexual genetic make-up. All that can be inferred from it is whether an individual does or does not carry two X chromosomes; it does not show whether the normal Y chromosome is present, a point of some importance when a patient presents with some male and some female sex characters. Then three years ago J. H. Tjio and A. Levan[3] in Sweden, and C. E. Ford and J. L. Hamerton[4] in Great Britain, discovered that the diploid chromosome number in man was 46 and not 48 as had long been supposed. This finding was made possible by better techniques both in the preparation of the cells and in their staining.[5,6] The new techniques have in fact made possible not only the accurate counting of human chromosomes but also the recognition of some of the individual pairs, and it is this knowledge which is now being applied to clinical medicine.

In 1959 Patricia A. Jacobs and J. A. Strong,[7] in Edinburgh, described a patient with the classical features of the Klinefelter syndrome (that is, an apparent male but with gynaecomastia, small testes, poor facial hair growth, and a high-pitched voice). The nuclear sex chromatin was typical of female cells (chromatin-positive), and the chromosome number in bone-marrow was 47 instead of 46. The additional one was considered to be an extra X, and the individual to have the constitution XXY.

The next discovery, also made this year, was of great importance and came from J. Lejeune and his colleagues,[8] in Paris. They found that each of three mongol boys had 47 chromosomes, but here the additional structure was a small acrocentric autosome and not either of the sex chromosomes. This finding has been confirmed by Jacobs and her colleagues.[9] Six typical mongols, 3 males (chromatin-negative) and 3 females (chromatin-positive), were all shown to have the small extra chromosome. Confirmation of the abnormal findings was also obtained from study of the remarkable case reported by Professor L. S. Penrose and his colleagues; this was a child who exhibited features of both Klinefelter's syndrome and mongolism combined.[10] The authors of the report showed that, in 50 cells obtained from the bone-marrow of the patient, each contained 48 chromosomes, one of the extra ones being an X and the other the small additional acrocentric autosome. This appears to be the first time that a human being with two extra chromosomes has been described. In another report Ford and colleagues[11] showed that a patient with Turner's syndrome had another chromosome abnormality. The clinical picture is that of a stunted infantilistic girl with primary amenorrhoea and absence of secondary sexual characteristics. Many of the patients are chromatin-negative, and in the case described counts from bone-marrow showed only 45 chromosomes, the missing one being an X. This evidently explains the chromatin-negative finding.

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[16] Brown, S. W., and Hannah, A., *Proc. nat. Acad. Sci.* (*Wash.*), 1952, **38**, 687.
[17] Harnden, D. G., Briggs, J. H., and Stewart, J. S. S., *Lancet*, 1959, **2**, 126.
[18] Ford, C. E., Polani, P. E., Briggs, J. H., and Bishop, P. M. F., *Nature* (*Lond.*), 1959, **183**, 1030.
[19] Krivit, W., and Good, R. A., *Amer. J. Dis. Child.*, 1956, **91**, 218.
[20] Merritt, D. H., and Harris, J. S., ibid., 1956, **92**, 41.
[21] Carter, C. O., *Brit. med. J.*, 1956, **2**, 993.
[22] Stewart, A., *Proc. roy. Soc. Med.*, 1957, **50**, 251.
[23] Baikie, A. G., Court Brown, W. M., Jacobs, P. A., and Milne, J. S., *Lancet*, 1959, **2**, 425.

Furthermore, no Y chromosome was present, and the genetic constitution of the patient was therefore XO.

The explanation of the abnormalities in the Klinefelter and Turner syndrome seems to be that non-disjunction (failure to separate) of the sex chromosomes has occurred at cell division. In the case of the Klinefelter syndrome this means that at meiosis the X chromosomes fail to separate from each other and instead both go to the same end of the spindle. One egg therefore receives two X chromosomes and the other none. If the former is fertilized by a Y-bearing sperm the result will be a case of Klinefelter's syndrome (XXY). If it is fertilized by an X-bearing sperm, the result could be the "super female" (XXX) known in *Drosophila* and now recently described in man.[12] The egg with no X chromosomes would result in a person with Turner's syndrome if fertilized by an X-bearing sperm, and the fourth possibility, YO, would almost certainly be lethal. Both Klinefelter's and Turner's syndromes could also be caused by non-disjunction occurring during the formation of spermatozoa, one of a pair of these gametes being XY and the other O.

The XO constitution of many patients with Turner's syndrome explains why, though females, they have the high frequency of red-green colour blindness (about 8%) characteristic of males. The gene for this condition is a sex-linked recessive on the X chromosome, and, as in the colour-blind male (XY), there is no normal allele to mask it. Professor Nowakowski and Drs. J. S. S. Stewart and P. E. Polani described at the K.C.H. symposium colour-vision studies in Turner's and Klinefelter's syndromes. These suggested that in the former it is the father who is at fault, transmitting O rather than X or Y; in the latter the chromosomal abnormality is in the mother, who hands on XX instead of a single X. If indeed the Klinefelter's and Turner's syndromes are formed by non-disjunction of the sex chromosomes, there should be equal numbers of both conditions in the population provided YO and XXX are lethal. In fact, the Turner cases appear to be commoner than the Klinefelter, but this may be because the former are more apt to seek medical advice. It is worth noting that sexual abnormalities superficially resembling Turner's syndrome may occur in patients with a normal sex-chromosome complement.[13]

A point of interest is that the Y chromosome can no longer be regarded as functionless but must have masculinizing properties, otherwise a Klinefelter individual would look more like a female. In this respect man differs strikingly from *Drosophila* (where XXY is a fertile female) and more closely resembles the system found in the rock plants of the genus *Melandrium*.[14] Some confirmation that this is so comes in a recent study by J. M. Tanner and colleagues[15] of growth rates in children with Klinefelter's and Turner's syndromes.

The extra chromosome in the mongols discovered by the French workers is the most fascinating problem of all. Non-disjunction in an autosome might be the explanation, causing one pair to become trisomic; or alternatively the extra structure might be a "supernumerary." However, by analogy with other organisms the former seems much more likely, since supernumeraries are usually inert, and this is clearly not so in the case of the mongol. Furthermore, in *Drosophila* there is a hint that increasing maternal age may initiate abnormalities in chromosome number,[16] and it would be worth while noting if maternal age is related to the frequency of Turner and Klinefelter syndromes as it is to that of mongols. L. Lejeune also reported at the K.C.H. symposium the probable finding of only 45 chromosomes in a child suffering from low intelligence and multiple bony abnormalities of the skull and spine (polydyspondylism), but, as D. G. Harnden reported, other likely conditions such as anencephaly,[17] neurofibromatosis, and epiloia have so far given normal chromosome patterns.

It is worth remembering that non-disjunction can occur not only at meiosis but at mitosis any time after the formation of the zygote. It is therefore possible to have a condition of mosaicism in which some cells have their normal complement of chromosomes and others 47, and a patient with Klinefelter's syndrome presumed to be of this type, some of the cells being XXY and some XX, has indeed been reported by Ford and colleagues.[18] Thus the mongoloid traits occurring in normal individuals might have been caused by non-disjunction taking place late in the formation of the embryo. The next steps will therefore surely be, firstly, to investigate other known trisomic organisms to determine the exact effect of the extra chromosome, and, secondly, to see if there is any evidence of mosaicism in man in individuals normal except for minor mongoloid traits. Finally, the problem of leukaemia is being studied in relation to chromosomes. The trisomic condition in mongols is of course present in their leucocytes, and it has been shown that mongols are more susceptible to leukaemia than normal people.[19–22] Now chromosomal abnormalities have been reported in four out of five cases of acute leukaemia, though not in cases of chronic leukaemia.[23]

ANOTHER WINTER OF BRONCHITIS

With the onset of another winter, the bronchitic population is beginning to wonder once more what is in store for it. Roughly a million persons in Britain have respiratory symptoms which can be accounted for by the bronchitis–asthma–emphysema group of diseases, principally men over the age of 40 years. Of these, some 15,000–20,000 are likely to die during the next six months, and many more will emerge with increased respiratory disability.

Each sufferer from bronchitis must decide on the risks and precautions he is prepared to take. When symptoms are mild, such as a little early morning cough and sputum and a tendency to wheeze after colds in the head, the reduction or abandonment of smoking may suffice to eliminate them. Most people have a critical age beyond which tobacco provokes excessive mucus, but habitual smokers are always tempted to prolong their addiction until a real disability develops. The climatic conditions which most often aggravate bronchitis are fog, dampness, and cold, in that order. Here again, the precautions to be taken are a matter of individual responsibility. One man may be able to control the temperature of his garage, his car, and his office, and, provided he avoids acute upper respiratory infections, may be able to withstand much unfavourable weather. Another may purposely undertake sheltered work of less responsibility than previously in order that he may protect his chest and remain at home on foggy days. Less fortunate is the man with bronchitic attacks in winter who dare not stay away for fear of losing his job. These differences, which are largely economic, require careful medical assessment, due regard being paid to the previous history. Exposure to a polluted fog may entail weeks of avoidable illness ; on the other hand, many bronchitics have the will-power to maintain a reasonable sickness record in spite of their chests. It is no exaggeration to say that bronchitics study the weather from day to day.

Bronchitis, asthma, and emphysema all contribute to obstruction of the airway, which is greatest during a forced expiration. By holding their chests in a state of permanent inspiration, in which the air passages are dilated, many bronchitics find that they are able to breathe quietly and sustain their tidal respiration without a wheeze, but as soon as they exert themselves too much and breathe more deeply the depth of expiration exceeds the threshold of the wheeze and dyspnoea occurs, often with paroxysmal coughing. Hence they must learn the significance of the threshold of wheeze. If, in addition, they can master diaphragmatic and lateral thoracic breathing, they will greatly extend the circumstances in which tidal respiration can be maintained without conscious effort, avoid much unnecessary distress, and be able to choose the most convenient times to attempt expectoration.

Asthma, or reversible airway obstruction, troubles most bronchitics sooner or later. One or other of a combination of ephedrine, aminophylline, and isoprenaline usually affords some relief, particularly in the earlier stages of the disease. The recently introduced inhalations of pancreatic enzymes seem often to ease expectoration temporarily, but their repeated use may prove to be disappointing.

Measures for the prevention and suppression of acute respiratory infections remain problematical. Many bronchitics avoid close contact with anybody having a cold in the head, even to the point of social rudeness. Others demand a vaccine, possibly of mixed influenza viruses ; these are type-specific, but they cannot reasonably be withheld by medical practitioners, because they afford a measure of protection in a subsequent outbreak provided the appropriate virus has been included. Mixed anticatarrhal bacterial vaccines seem sometimes to protect mild bronchitics, but their value in the moderately and far advanced stages is very doubtful ; autogenous vaccines have little or no advantage over standard preparations.

The chemotherapeutic control of bronchitis has been the subject of much study in recent years. These agents can do no more than suppress or destroy bacteria in the air passages, whose existence there depends on excessive mucus which cannot be easily expectorated and which protects them from leucocytic invasion. The choice of a suitable drug must depend primarily on its effect on the likeliest pathogenic bacteria. Available evidence strongly suggests that *H. influenzae* and, to a less extent, the pneumococcus are the most important pathogens. The pneumococcus is readily susceptible to a wide range of antibiotics and also to sulphonamides, but *H. influenzae* is not, which accounts for the disappointing results of long-term trials of prophylaxis with penicillin and sulphonamides. Both *H. influenzae* and the pneumococcus can be overcome with the tetracyclines, chloramphenicol, and erythromycin. Repeated or continuous courses of chloramphenicol may induce blood dyscrasia, and erythromycin should be held in reserve for resistant staphylococcal infections in general. The tetracyclines, which are often less effective than either of the other two in individual patients, remain. Most clinicians are agreed that tetracycline itself is preferable to the

oxy- and chlor-derivatives; the newly devised but not yet generally available de-methyl-chlortetracycline may possibly become the preparation of choice.

The principal indications for treatment are exacerbations of infection and a purulent sputum during remissions. For the former, treatment is likely to be started earliest if patients are allowed to have a supply of tetracycline tablets to hand. Some patients find that this is not enough and that a small maintenance dose through the winter saves much sickness absence. The aim should be to give as little as is effective, 0.25 g. twice a day often being sufficient. Bronchitics with a profuse purulent sputum need more, but they also require careful assessment in case other conditions such as bronchiectasis coexist.

THE BARNET VENTILATOR

The recent widespread publicity in the press about "a new electronic lung to replace the iron lung" is commented on in this week's correspondence columns by Dr. W. H. Kelleher, who speaks with authority on the use of such apparatus for patients disabled with poliomyelitis. Press publicity was supported by similar publicity over the radio and television. The public—and the medical profession—were thus led to believe that an important scientific advance had been made. There is, we are reliably informed, nothing novel in the Barnet ventilator, which is no more than a further addition to the number of machines available for positive-pressure artificial respiration—a method that was introduced in Denmark in 1952 and has been used in this country since 1953. An earlier model of the much-publicized Barnet ventilator was described by Rochford, Welch, and Winks,[1] and is one of the many referred to in a book published earlier this year.[2] The machine consists of a time-cycled switch to which air or gases are delivered under pressure. This is not a new arrangement, and has, moreover, certain disadvantages, some of them referred to in Dr. Kelleher's letter.

This is yet another of many recent examples whereby firms of one sort and another have gone out of their way to publicize their medical wares direct to the lay press. Representatives of the press are not always in a position to assess the claims made on behalf of this vaccine, that drug, or the other apparatus. Doctors themselves are naturally bewildered by this publicity, and on top of it are subjected to demands of their patients for the latest new thing thus widely advertised in the market place. Firms who lend themselves to this kind of activity should realize that it is apt to have a boomerang effect.

[1] Rochford, J., Welch, R. F., Winks, D. P. (1958). *Brit. J. Anaesth.*, **30**, 23.

[2] Mushin, W. W., Rendell-Baker, L., Thompson, P. W. (1959). *Automatic Ventilation of the Lungs*. Blackwell, Oxford.

ADVERTISING 'FLU

The medical profession was somewhat surprised to learn early in October that Dr. H. Beric Wright, according to press reports, was advising members of the Institute of Directors—as head of their medical research unit—to have their staffs inoculated with an influenza vaccine said to be a mixture of the various strains of the three predominant influenza viruses. In a leading article in the *Journal* of October 17, referring to the possibility of an influenza epidemic this winter, we observed that "on the whole the omens are not too bad." In the same leader we said: "We are at a loss to discover the basis for alarmist prophecies recently appearing in the lay press," and questioned the advisability in any case of giving polyvalent vaccines, suggesting that a good compromise might be "a bivalent vaccine containing A2 and B components."

Last week we received a handout from a public relations firm headed "Anti-flu Initiative by Advertising Agency." This handout began by saying that doctors predict an influenza epidemic this coming winter and that a number of firms have taken advantage of the inoculation facilities provided by the medical research unit of the Institute of Directors. The handout informed us that the London staff of an advertising agency had voted 70% in favour of the inoculation, and the public relations firm informed us that we could obtain a photograph on request. It is here reproduced with the caption supplied to us.

Photonews, Ltd.

Mr. J. F. Preston, Managing Director of Ripley Preston and Co. Ltd., of Cheapside House, Cheapside, E.C.2, having his anti-influenza injection from Dr. Beric Wright, of the Research Department of the Institute of Directors.

There are a number of aspects about this that must be disquieting, not only to individual doctors who, through this publicity, are besieged by patients for one of the influenza vaccines that are available, but also to those to whom the profession and public look for guidance on campaigns for prophylactics. The Ministry of Health at the centre, the medical officers of health at the periphery, and general practitioners, may wonder just where all this kind of thing is going to lead to. It is notoriously difficult to be dogmatic about the behaviour of influenza, but, according to the most authoritative advice we could obtain, we concluded in

the leader of October 17 that there was no cause for alarm. Later the Ministry of Health issued a statement on October 19 that what information and expert advice it had received suggested that there was no indication of the likelihood of a major epidemic of influenza in the country during the coming winter. The prediction of an epidemic may turn out to be right, but there seems to be little sound basis for it.

The Institute of Directors is having a field day this week at the Festival Hall, when at the price of a 4 gns. ticket its members will be told about the dangers of high-pressure living by a selected group of doctors. There doesn't appear to be anything in the programme about the dangers of high-pressure advertising, a subject we suggest might usefully be taken up by its medical research unit.

C.M.O.'s REPORT

During the 100 years or so up to 1950 the expectation of life at birth increased in Great Britain, as in many other countries. But since then it has not changed much, being now about 68 years for males and 74 years for females. This is because the treatment of neoplastic and degenerative cardiovascular diseases has not equalled the successes achieved in treating the infectious diseases. Drawing attention to this in his latest report,[1] the Chief Medical Officer of the Ministry of Health discusses an attempt that has been made elsewhere to combat the various types of malignant disease by means of special centres for the detection of cancer. Apparently by 1949 over 250 such centres were operating in the U.S.A. A serious difficulty proved to be that the number of cancers detected early "was quite disproportionate to the outlay," and annual repeat examination "soon overwhelmed the staff to the exclusion of any new patients." No centres have been opened in Britain, for the C.M.O. reports that the idea has not found favour here: "It is now realized that such centres cannot hope to solve any public health problem and that they are prohibitive in staff."

The report includes a special section (by Dr. W. H. Bradley and colleagues) on rabies, for, though the disease is very rare in Britain, only constant vigilance makes it so. Two cases have been reported since 1951; in both the infection was contracted on the Indian continent. The last case to have resulted from infection in Britain was in 1911, when a master of foxhounds died from what was considered to be rabies some months after being bitten by a fox. Canine rabies was brought under control in 1902 after a troublesome period of endemicity. The illegal importation of an infected dog reintroduced the disease in 1918, so that between then and 1921, when it was again eradicated, there were 316 cases in dogs, two in horses, and one in a pig. Another disease, formerly endemic in Britain and now only imported, is leprosy, of which about 280 cases are known to the Ministry; all these patients contracted the disease abroad. The source of infection is sometimes impossible to trace precisely, but the report adds: "It is not, however, easily communicable to adults, and much of the apprehension felt by the public and even by some members of the medical profession regarding the risk of infection is groundless. Comparatively simple precautions will render most patients innocuous even to their families. These precautions involve the avoidance of close contact with others, especially children, and the provision of cooking vessels and tableware for the patient's exclusive use."

In contrast to these rare imports stands the common cold and its congeners, on which the report includes a useful review (by Dr. A. T. Roden). The morbidity survey in general practice, organized by Dr. W. P. D. Logan and colleagues at the General Register Office, has shown that the common cold causes more consultations between patient and doctor than any other disease. A great variety of allied diseases, mainly respiratory, are caused by viruses that are gradually being differentiated from each other, and the report comments that "the immediate prospects of unravelling this complex group of illnesses have seldom appeared brighter."

[1] *Report of the Ministry of Health for the Year 1958*, Part II, 1959. H.M.S.O.

CONTROL OF ANTHRAX

Anthrax is an uncommon disease in Great Britain, and the frequency of it has been declining for some years. But it should be possible virtually to eliminate it. A useful report on how this might be attempted was published last week. It followed closely on a widely publicized warning, which proved to be a false alarm, that some meat sold by a pets shop was from an animal that had died of the disease. This is a possible, though very unlikely, contingency, and had the meat been infected the infection could have passed to people handling it.

In 1957 the Minister of Labour set up a committee[1] [2] to recommend any provisions that might be necessary to improve the control of imported goods likely to be infected with anthrax. The statistics given in the report[3] show that in the four years 1955–8, 53 cases in Great Britain were notified to the Chief Inspector of Factories. The annual totals are about a quarter of those notified before the first world war and about half the totals notified between the wars. The proportion of cases ending fatally has also declined—mainly owing to the introduction of penicillin—and for the years 1955–8 was 5.7%. Some cases not covered by the Factories Acts, and so not reported to the Chief Inspector, also occur; they may be about as numerous as those that are reported, for the Registrars-General record about twice the numbers of deaths as does the Chief Inspector. There were six in Great Britain in 1950–4 (of which the Chief Inspector recorded three).

[1] Members: Mr. R. F. Levy, Q.C. (chairman), Professor A. K. Cairncross, C.M.G., Mr. T. Eccles, J.P., Mr. J. B. Solomon, Dr. A. J. H. Tomlinson.
[2] *Brit. med. J.*, 1957, **1**, 574.
[3] *Report of the Committee of Inquiry on Anthrax*, 1959, Cmnd. 846, H.M.S.O., London. 12s.
[4] Lamb, R., and Maclean, E. S., *Brit. med. J.*, 1957, **2**, 191.
[5] —— *Lancet*, 1958, **2**, 151.
[6] Green, D. M., and Jamieson, W. M., ibid., 1958, **2**, 153.
[7] *Brit. med. J. Suppl.*, 1959, **1**, 172.

Thus the committee concludes: "It cannot be said that any serious public problem is now presented by the disease."

Since the only important source of anthrax in Britain is the products of infected animals imported from abroad, the committee makes a number of recommendations designed to retain or tighten control on the imports. These are detailed technical measures concerned mainly with the import from some Eastern countries of wool and the hair and skins of goats, horses, and camels. Several cases of anthrax due to infected bone meal have been seen in recent years,[4–6] but the committee does not think they are numerous enough to need special requirements for sterilization of the material, though it recommends keeping a watch for such cases. Dockers should be specifically warned of any anthrax risk and carry a prescribed anthrax card. the committee suggests, and special arrangements should be made in industry for the early detection and treatment of cases when possibly infected material is handled. Outside the industrial scene the committee recommends that anthrax should be made a notifiable disease under the Public Health Act. This view is in agreement with that recently advocated by the B.M.A.[7]

DANGER OF CORTICOSTEROIDS IN OPHTHALMOLOGY

The value of corticosteroids in ophthalmology has been so great and their beneficial effects so definite in the treatment of iridocyclitis, post-traumatic inflammations, and allergies of the lids and conjunctivae, that the dangers are apt to be overlooked. During the past year, however, several letters emphasizing the dangers have appeared in this *Journal*.[1–3] As is true elsewhere in the body, corticosteroids applied to the eye reduce resistance to the spread of infection and also delay healing by fibrosis. Further, their use may so diminish the signs and symptoms of disease as to confuse the diagnosis. Corticosteroids are invaluable in the treatment of the allergic forms of corneal ulceration, as for example in rosaceal keratitis. But they should never be applied in cases of infective corneal ulceration unless combined with an effective antibiotic. The most dangerous practice is the application of topical corticosteroids in the treatment of virus infections of the cornea.[4 5] No matter whether applied alone or in conjunction with antibiotics, the result will be the same, since viruses are unaffected by any antibiotic.

Dendritic ulceration (herpes simplex corneae) is the most common of the virus infections of the cornea. In its early stages the infection is confined to the epithelium, and chemical cauterization at this stage will eradicate the infection. But the administration of cortisone will hasten the spread of the virus within the epithelium while at the same time reducing the warning symptoms. Furthermore, cortisone will increase the likelihood of the virus invading the substantia propria of the cornea and will predispose to infiltration of the deeper layers. If this occurs, the disease will run a protracted course and a dense and permanent corneal opacity will result. It follows, therefore, that corticosteroids either alone or in conjunction with antibiotics should never be applied to the eye until a definite diagnosis has been made.

[1] Abrams, J. D., *Brit. med. J.*, 1959, **1**, 1116.
[2] Jackson, C. R. S., ibid., 1959, **1**, 1300.
[3] Fox, D. B., ibid., 1959, **1**, 1300.
[4] Tucker, D. P., *New Engl. J. Med.*, 1958, **258**, 946.
[5] Thygeson, P., Kimura, S. J., and Hogan, M. J., *A.M.A. Arch. Ophtha'.*, 1956, **56**, 375.

DOCTORS INGENIOUS

The Doctors' Hobbies Exhibition is with us again, a further reminder of the ingenuity, even the fanaticism, with which doctors pursue their astonishingly diverse pastimes. The exhibition, organized by Messrs. Bengers and held at B.M.A. House, is now a firmly established event. Gone are the uncomfortably darned socks, the knobbly knitted jumpers, and weird inventions that marked the first exhibition in 1957. Now there is a far higher standard in the exhibits on view—but no less diversity. There are the inevitable stamp collections, photographs, home-made wines, model aeroplanes, and water-colours—but it is the numerous oddities that one remembers: a sheepskin hat made from home-cured skins, two bantams, a folding fishing-line dryer, a portable television set of midget size, a steam-power plant for a model cable ship. The most macabre exhibit is probably the shrunken head of a Jivaro Indian, but there is also a collection of fishes' ears, two silver Regency nipple-shields, a coffee-pot cosy, and a tango in D minor; a single-decker motor-coach artfully converted into a luxury caravan for family holidays, a catamaran yacht, and a trimaran yacht, a Tibetan prayer-wheel, a picnic basket made of two plastic sink-tidies, ships in bottles, knights in armour, with a swarm box for your bees, the entrance labelled BEES THIS WAY PLEASE, and an exhibit on esperanto to help doctors speak the same language.

First prize this year went to Dr. R. C. Bell, of Newcastle upon Tyne, for his book *Board and Table Games*, a fascinating and erudite history which is shortly to be published by the Oxford University Press. The second prize went to Dr. C. E. D. H. Goodhart (Carshalton Beeches) for a splendid collection of seventeenth-century samplers; and the third to Mr. R. C. Murray, of Inverness, for a Burraesque painting, *Return to Consciousness*, depicting the patient's-eye view.

But most visitors will want to award their own personal prizes: the technique for making a 1902 Caruso record sound like an up-to-date recording will be a sure attraction for the many who possess a device which does the same thing but in the opposite direction. Admiration mixed with envy will be the main response to almost all the entries in the Home Handyman Section, and it will be with the usual itching fingers that visitors of any age will contemplate Dr. R. P. Hendry's immense, complex, populous, and richly detailed model railway.

Clinicopathological Conference

A CASE OF RHEUMATOID ARTHRITIS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

The last Clinicopathological Conference (*Journal*, September 26, p. 559) concerned a man with a rare chronic disease—paroxysmal nocturnal haemoglobinuria—of which there are fewer than 100 recorded cases. This week's case is of a much commoner malady—rheumatoid arthritis, which affects about one in every fifty of the adult population. Two features of this case are interesting; first, the patient was cared for at Hammersmith Hospital for nearly 20 years, from the onset of the disease to her death; and, second, she came to necropsy never having had steroid hormones systemically—an unusual event these days (Case No. 189,178; P.M. No. 8,224).

Clinical History

Dr. A. St. J. DIXON: This patient, a married woman, aged 71, was admitted to Hammersmith Hospital on five occasions between 1944 and 1957. Her disease started

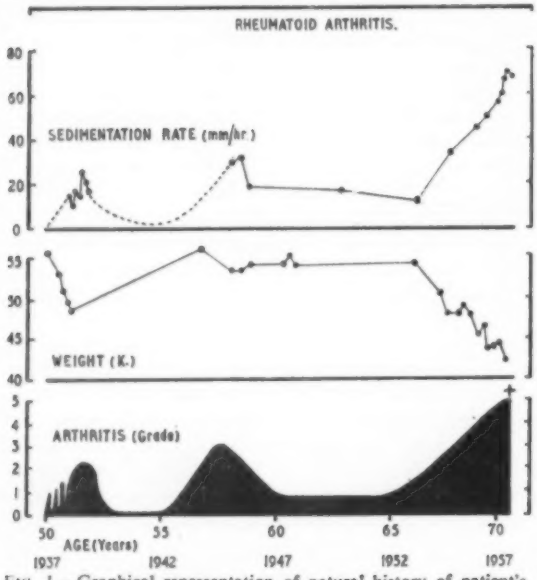


FIG. 1.—Graphical representation of natural history of patient's rheumatoid arthritis over 20 years.

in 1937 when she was 50 (Fig. 1). Before this she had been quite well. Early that year she experienced recurrent acute attacks of joint pain and swelling, principally affecting her ankles and the great toes. After several attacks, however, the arthritis failed to clear from the involved joints, and spread to her knees, hands, wrists, and elbows. Her weight fell by approximately one stone (6.4 kg.) to 8 st. 5 lb. (53 kg.), and she felt generally ill. She attended the out-patient department for the first time in November, 1937. It was noted that the nature of her disease at its onset, with episodic arthritis and attacks in the great toes, resembled gout. However, the serum uric acid estimation was normal.

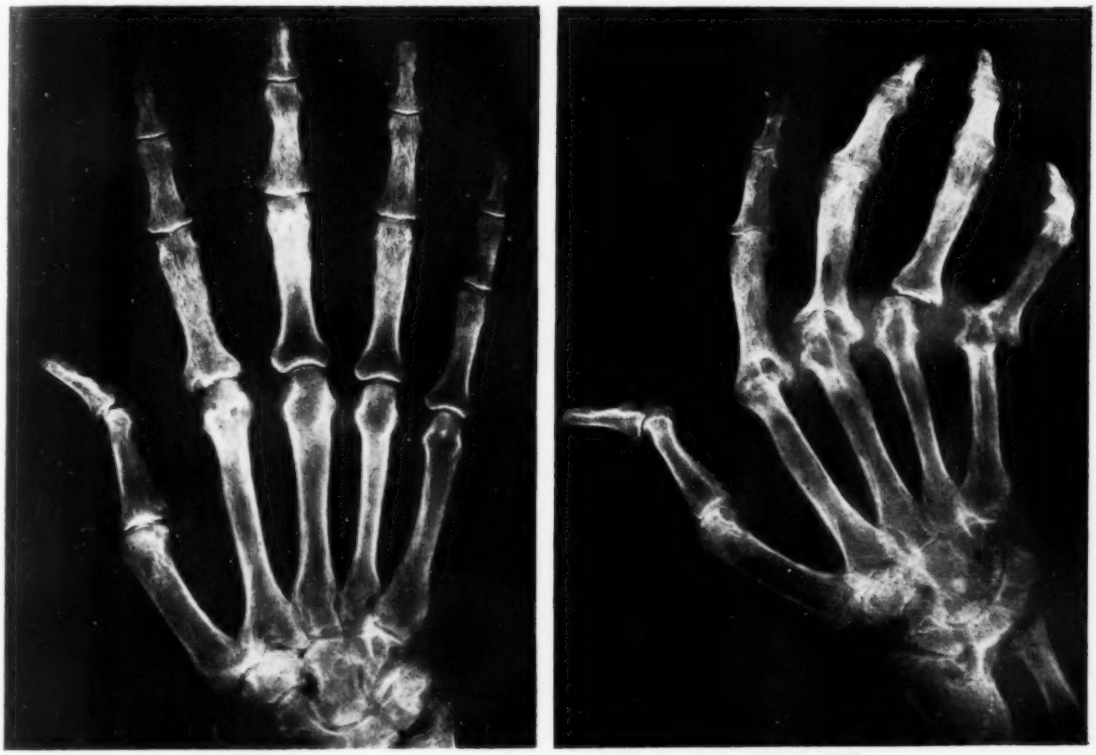
Gout is, of course, rare in women, and exceedingly rare before the menopause. This patient had had her menopause some four years earlier, so gout was certainly a possibility. Nevertheless, the degree of constitutional illness, particularly the amount of weight lost, would have been against gout. The diagnosis of rheumatoid arthritis was made later. She was treated with physiotherapy, and, in accordance with the custom of the time, sent for a dental check-up. It is also interesting to note that she took part in a controlled trial of gold therapy and received monthly injections throughout 1938. After this her disease went into a complete and prolonged remission, lasting until 1942. The moral of this story, however, is that she was, as it happened, a control case, and received blank injections.

RECURRENCE OF ACTIVITY

In 1942 her disease recurred with rather more severe disability, but she did not attend hospital again until 1944. By this time her right knee was the most severely involved joint, and she was admitted for a diagnostic aspiration. About 20 ml. of a turbid, yellow, sterile fluid was removed. This is typical of rheumatoid joint fluid, which usually contains a lot of polymorphonuclear leucocytes and looks like thin pus instead of the clear, viscous, and highly lubricating normal joint fluid.

Subcutaneous nodules appeared on the elbows in 1945, and several of these were removed. Their histology was typical of rheumatoid nodules (Fig. 2). Between 1948 and 1953 her disease was again in good symptomatic remission, and she was doing all her housework and needing no treatment. Residual changes were, however, present in the hands. In 1950 her weight had risen to 9 st. 5 lb. (59.5 kg.). An electrocardiogram at this time (for "tightness of the chest") was said to be suggestive of ischaemia, but in retrospect was probably within normal limits. From 1953 symptoms worsened. An injection of intra-articular hydrocortisone into the right knee gave relief lasting a year, but other joints deteriorated. By 1954 her weight had fallen to 8 st. 5 lb.

FIG. 2.—Subcutaneous rheumatoid nodule, showing area of collagen degeneration ringed by histiocytes and fibroblasts, with a small blood vessel on the right. (×117.7.)



SEPT. 1950 AUG. 1957

FIG. 3.—Right hand showing the progress of the deformity between 1950 and 1957.

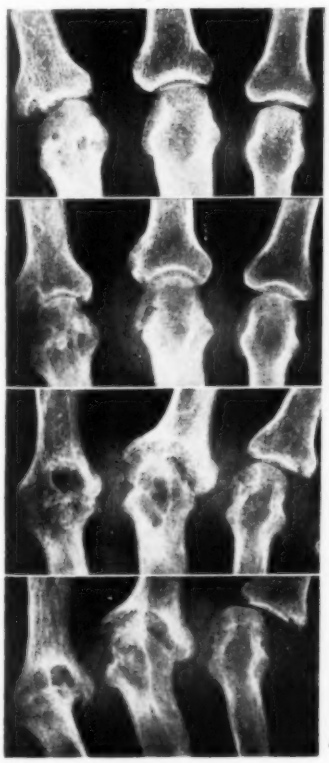


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FIG. 4.—Enlargement of right 2nd, 3rd, and 4th metacarpophalangeal joints to show the successive development of destructive juxta-articular erosions and subluxation.

FIG. 5.—Lateral view of the dorsal spine to show osteoporosis and wedging of the 5th and 6th vertebrae.

FIG. 7.—Passive congestion of liver with pooling of blood in centrilobular zones and disappearance of hepatic cells. (×31.5.)

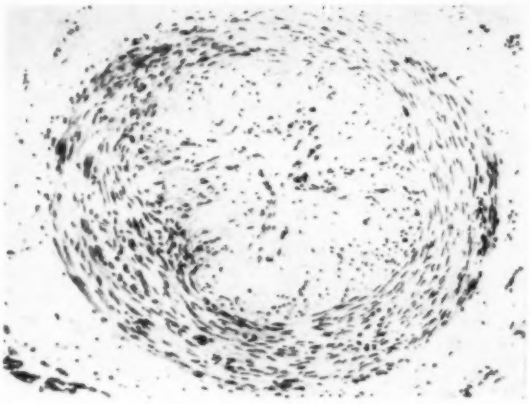

FIG. 8.—Digital artery showing internal fibrous thickening. (×113.) The black clumps towards the centre represent haemosiderin granules clustered in macrophages.

FIG. 9.—Metacarpophalangeal joint 5th finger (left). (×7.7.) Note the irregular fibrous synovial thickening opposite the joint space on the left of the photograph.

FIG. 10.—Metacarpophalangeal joint 3rd finger (right). (×7.7.) Highly disorganized joint with extension of synovial pannus over articular surfaces. Fragments of articular cartilage lie in the joint space.

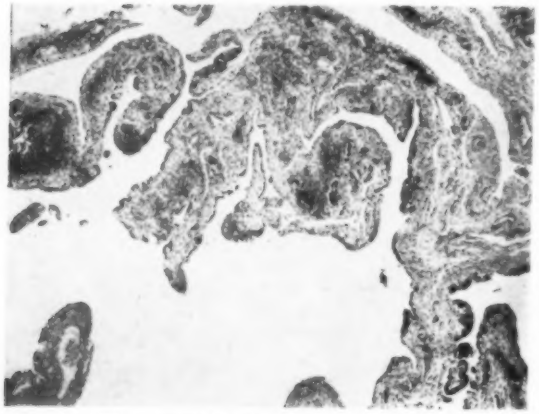

FIG. 11.—Villous synovitis knee-joint. (×31.5.) Small foci of lymphocytes are conspicuous in the enlarged villi. There is a large compact focus to the left of the photograph.

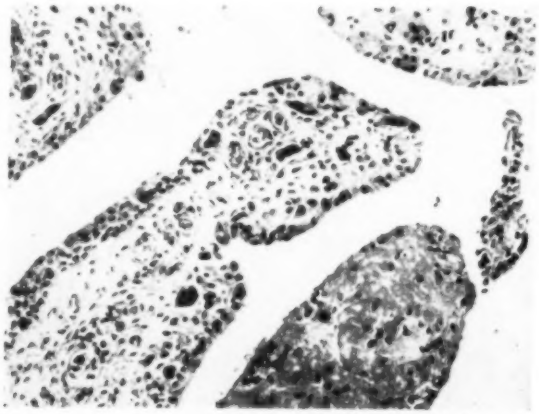

FIG. 12.—Heaping up of the synovial intimal cells in the knee-joint with many multinucleated cells. (×113.)

(53 kg.) and her disability increased so that she became unable to get in or out of the bath. One by one her abilities were taken away by the advancing disease, and by January, 1956, she was very considerably crippled. Her sedimentation rate had risen and her weight had now fallen to 7 st. 6 lb. (47.2 kg.). Her hands were swollen and painful. She also showed generalized enlargement of lymph nodes and the spleen was palpable. Amyloidosis was suspected, but not confirmed by an intravenous congo-red test, which gave a one-hour dye retention in the plasma of 69%—a figure on the low side of normal, but common in rheumatoid arthritis without evidence of amyloid. Moreover, moderate enlargement of lymph nodes is quite common in uncomplicated rheumatoid arthritis, without necessarily signifying amyloidosis. The nodes usually enlarge regionally—that is, in the drainage areas of the most affected joints. In such cases the histology shows only a non-specific hyperplasia. Similarly, a moderate enlargement of the spleen can occur quite non-specifically in uncomplicated rheumatoid arthritis, although it is not as common as most textbooks would have one believe.

Further Deterioration

In November, 1956, she was readmitted to hospital for eight weeks, for general ill-health. Her weight was now 6 st. 5 lb. (40.4 kg.) and her arthritis was active. She was found to have a collapse and infection of the lower lobe of the left lung, which responded to treatment with penicillin. A rough basal systolic murmur was first noted, described as "ejection type," meaning that it was accentuated in mid-systole. *X*-ray examination of the chest at this time showed some calcification of the aortic knuckle. She improved in hospital, but deteriorated further after her discharge in January, 1957. The outstanding feature then was the development of numerous subcutaneous nodules on almost all bony prominences, and even on the ears. In August, 1957, she had to be readmitted because of mild cardiac failure. She was tired, somewhat breathless and the jugular venous pressure was +1 cm. above the sternal angle. The blood pressure was 160/90 mm. Hg. Several of the nodules had ulcerated and others looked as though they might do so at a later date. It was thought better to substitute a clean surgical incision for a spontaneous ulcer, and some of the more superficial nodules which had not ulcerated were removed. The opportunity was taken to inject some local hydrocortisone acetate into the centre of one nodule before removal, to see if this method could be used to control excessive nodule formation in this patient. Unfortunately, an incision became infected and healing was delayed. She was given digitalis and various antibiotics, and was allowed to go home, with the incision still not quite healed. Electrocardiograms at the time showed ischaemic changes, but no evidence of pericarditis.

Terminal Illness

This brings the story up to her last illness. After her discharge she was supervised from the out-patient department. On October 28, 1957, she was found to be in cardiac failure again. The jugular venous pressure was now +3 cm., despite digitalis. Some adjustments were made to her therapy and she was allowed to go home. One week before her final admission she felt weak, and retired to bed. She noted pain in the right upper abdomen, worse on breathing. She vomited several times and became more breathless. Her husband, who had always been mentally unstable, was removed to a mental hospital about this time and she was left largely to her own devices. She took little or no solid food, and for three days prior to admission stopped taking digitalis. She was readmitted as an emergency on November 19.

There were no individuals with arthritis in her family, and her previous medical history was not relevant except for an attack of left-sided pleurisy in 1940.

On examination she was a thin, frail, elderly lady with a normal temperature, who was breathless and distressed. Her extremities were cold and blue and her pulse weak, rapid, and regular. The jugular venous filling pressure was increased to the angle of the jaw. The blood pressure was reduced at 110/80 mm. Hg. The apex beat was felt in the fifth space in the anterior axillary line. The cardiac impulse was tapping and a third heart sound was heard at the apex. There were no murmurs or rub. There was impaired resonance at the left base and rales at both bases. Subcutaneous nodules were present over elbows, knees, hands, scapulae, and the right ear. Small vascular necroses were present in the skin of the fingers. There was a mild dorsal kyphosis with some scoliosis. There were many rheumatoid changes in almost all joints, including swelling and deformity of the proximal interphalangeal and metacarpo-phalangeal joints with ulnar deviation, swelling and limitation of movement in the wrists, ankles, mid-tarsal joints, and forefeet, small flexion contractures of elbows and knees, especially the right knee—and severe restriction of movement in the cervical and dorsal spine.

Investigations

Various investigations were done during the final two admissions. The significant findings were: *Urine.*—Contained *Bact. coli* but showed no albumin. *Blood.*—Haemoglobin 10 g./100 ml.; mean corpuscular haemoglobin concentration 29.5%; white-cell count—total 4,000 cells/cu.mm., differential count normal; serum albumin 3.3 g./100 ml.; serum globulin 4 g./100 ml. Electrophoresis showed a non-specific $\alpha_2\beta$ globulin increase. Thymol turbidity 9 units; zinc sulphate turbidity 9.6 units. Sedimentation rate (Westergren) varied from 50 to 74 mm. in one hour. Differential sheep-cell agglutination test for rheumatoid arthritis, positive at 1 in 128 dilution. Blood urea, 22 mg./100 ml.

X-ray examination showed the advance of rheumatoid changes in the hands (Figs. 3 and 4), knees, and feet. All bones were osteoporotic, and there was wedging of the fifth and sixth thoracic vertebral bodies (Fig. 5). No chest radiograph was taken on the terminal admission: a film two weeks before had shown a generalized increase in lung markings and no enlargement of the heart.

The electrocardiograms are best considered in sequence (Fig. 6). The record of August, 1957, shows a moderate degree of left ventricular hypertrophy. The

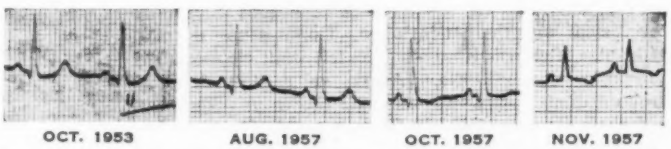

FIG. 6.—Sequence of electrocardiograms, lead II only, to show the development of T wave changes.

chest lead T waves are upright. In October, 1957, about a month before she died and when she was receiving digitalis, the record is much the same except that the chest lead T waves are diphasic, and she has a small Q wave in lead III which was not previously present. The final graph, on the night she died, shows a further change. There is tachycardia, low voltage, and widespread T wave inversion. It shows little, if any, evidence of S-T segment elevation or depression that one might associate with a current of injury due to recent pericarditis, and the graph was in fact reported as showing grade 2 left ventricular hypertrophy and/or postero-lateral ischaemia.

Staphylococcal Infection

The bacteriology of the biopsy wound is interesting. On September 12, 1957, penicillin- and tetracycline-sensitive staphylococci were present, and were still present nine days later despite penicillin treatment. On October 17 staphylococci resistant to penicillin and tetracycline were grown. Thus she had acquired the multiply resistant "hospital staphylococcus" during her stay.

She was given oxygen, digitalis, mersalyl, and penicillin for her terminal episode, but she rapidly weakened and died 12 hours after admission. The long-term management of her rheumatoid arthritis had rested squarely on aspirin. She had never had systemic steroid therapy.

Clinical Diagnosis

(1) Nodular rheumatoid arthritis.

(2) Osteoporosis and collapsed vertebral bodies.

(3) Congestive cardiac failure due to ischaemic heart disease.

(4) Possible lung infection, left lower lobe.

Post-mortem Findings

Dr. J. G. Azzopardi: The body was that of a frail, poorly nourished, elderly woman. There were severe rheumatoid deformities of the hands. The finger-tips were cyanosed. There was oedema over the sacrum and in the feet and legs.

The *pericardial cavity* contained 150 ml. of greenish-yellow pus in which lumps of fibrin were present; the epicardium was covered with fibrinous exudate. Staphylococci were cultured from the pericardial fluid. Part of the anterior wall of the left ventricle was firmly fixed to the parietal pericardium by old, fibrous adhesions. Each pleural cavity contained approximately 200 ml. of brown-yellow slightly turbid fluid at the bases. The rest of both pleural cavities was largely obliterated by dense, fibrous adhesions. The peritoneal cavity was normal.

The *heart* was normal in size and shape. The right atrium and tricuspid valve were normal. The right ventricle measured 4 mm. at the conus. Pulmonary valve and major pulmonary arteries and veins normal. The mitral valve circumference was slightly reduced (83 mm.); the valve cusps showed some fibrous thickening consistent with the patient's age. Commissures normal. Chordae tendineae normal. The left ventricle measured 18 mm. at the base. Aortic valve normal. The myocardium as a whole was pale brown in colour and of slightly softer consistency than usual. The *coronary arteries* showed many atheromatous plaques, some of them calcified, but without gross narrowing of their lumina. *Aorta* showed only slight atheroma. Microscopically there was an acute fibrinopurulent pericarditis caused by Gram-positive cocci with appearances in sections suggestive of staphylococci. (Confirmed by culture.) Organization of the exudate suggested a duration of about two weeks. There was focal myocardial scarring in the posterior wall of the left ventricle but not in other sections of the heart. There was slight vascularization of the posterior mitral cusp, consistent with the patient's age. There was no evidence of the rheumatoid lesions sometimes seen in the valves or myocardium in rheumatoid disease.* Root of aorta normal.

Larynx, trachea, and main *bronchi* were normal. The *right lung* was examined after perfusion with formalin, *the left lung* in the routine way. No consolidation or infarction was present, or evidence of emphysema. Fibrous scarring without calcification at the right lung apex was the only significant finding. Microscopically the upper lobes of lung appeared normal. The lower lobes showed some albuminous alveolar oedema with some iron-laden macrophages ("heart-failure cells"). There were a few small thrombi in the smaller pulmonary artery branches.

The *alimentary tract* was normal. The *liver* showed centrilobular congestion only; there was no evidence of amyloid disease. Microscopically the liver showed severe passive congestive changes with pooling of blood around the centrilobular veins and collapse of the hepatic reticulin framework (Fig. 7). The surviving liver tissue showed fatty change. The gall-bladder, biliary tree, and portal and hepatic veins were normal. The *pancreas* was normal macroscopically and microscopically.

Both *kidneys* had easily stripped capsules. The renal surfaces were smooth except for a scarred area at the upper pole of the left kidney. Renal cortical and medullary markings were normal. There was no evidence of amyloid disease. Microscopically the kidneys had a basically normal architecture. There was fibroelastosis of the arteries, to be expected at that age, but no evidence of amyloid disease. Renal arteries and veins were normal, as were the pelves, ureters, and bladder. The ovaries were small and fibrotic. The uterus contained several small, calcified interstitial myomata.

The *thyroid* was normal in appearance. The *adrenals* appeared normal. Microscopically there was a slight increase of fibrous trabeculation in the thyroid. A few large colloid-filled vesicles lined by flattened epithelium were present; otherwise the parenchyma was normal. Slightly enlarged, fleshy, discrete *lymph nodes* were seen in the main groups. The *spleen* was firm on section and normal in appearance; it showed no evidence of amyloidosis. Microscopically the spleen showed a follicular hyperplasia with prominent germ centres. The lymph nodes showed only a mild degree of reactive hyperplasia. The *vertebral bone marrow* was osteoporotic, with collapse of D.5 and D.6.

Sections through the skin of a *finger* showed the end-result of old thrombosis, organization and recanalization in a small artery in the subcutis. The intima showed a gross fibrous thickening with almost complete occlusion of the lumen. Siderophages were present in the thickened intima. The internal elastic

* Cruickshank, B., *J. Path. Bact.*, 1958, **76**, 223.

lamina was intact (Fig. 8). Though there was no evidence of arteritis at the point sectioned, the inference from these findings is that there may have been arteritis at some distance from it.* Several blocks from the *interphalangeal, metacarpophalangeal,* and *knee joints* were examined. The changes consisted of varying degrees of synovial villous proliferation and replacement of synovium by vascular fibrous tissue variably infiltrated with lymphocytes, plasma cells, and histiocytes. The articular cartilages were in part eroded by the synovial pannus growing in from the edges (Figs. 9 and 10). The adjacent bone ends appeared porotic. In the knee-joint, villous proliferation was prominent and there were many small, compact lymphoid foci without germ centres in the more bulbous villi (Fig. 11). These foci constitute perhaps the most reliable single diagnostic criterion in the histological identification of the disease.† Irregular proliferation of the synovial lining cells was also conspicuous in the knee-joint, and multinucleated cells in the lining were not infrequent (Fig. 12).

The *brain* was not examined (limited post-mortem).

Pathologist's Diagnosis

(1) Congestive cardiac failure.

(2) Mild ischaemic heart disease.

(3) Staphylococcal pericarditis.

(4) Widespread rheumatoid disease with destructive joint changes. Old pleuritis. Possible rheumatoid digital arterial lesion.

(5) Senile osteoporosis with vertebral collapse.

Discussion

Professor E. G. L. Bywaters: In the old days before cortisone and antibiotics, patients with rheumatoid arthritis died at the usual age, usually from the usual causes, including such diseases as heart disease and bronchopneumonia. With antibiotics and cortisone they now die from rather more bizarre conditions. This lady did not have cortisone, but she suffered from a "silent" infection which is very much like that we have seen in patients treated with cortisone. People with rheumatoid arthritis do in fact tend to develop, particularly when they are elderly, these silent infections, sometimes in joints, sometimes elsewhere. I think that there is no doubt, however, that in this case this particular infection was acquired in hospital.

Hospital Cross-infection

Dr. Dixon: I wonder if Dr. Barber would like to comment on the bacteriology at this stage?

Dr. Mary Barber: I would like to ask Professor Bywaters whether the infection was related to the injection of hydrocortisone into the nodules? It seems to me just possible that that may have helped the staphylococcus to get established and would help to delay healing.

Dr. Dixon: Actually, she had hydrocortisone injected into one nodule, but not into the other, and the infection was in the non-injected one. The infected nodule had previously been the better of the two.

Dr. Barber: I think this patient is certainly a case of hospital cross-infection, because the initial strain was sensitive to penicillin and then, about a month later, a strain resistant to penicillin and tetracycline, and partially resistant to streptomycin, was isolated. Such a change in the antibiotic sensitivity pattern I think would be almost unheard of in the course of a month, whatever the treatment, and so one must assume that the second staphylococcus was a different strain and was in fact the hospital staphylococcus. I thought, therefore, you might be interested to know the incidence of *Staph. pyogenes* of that type in the hospital in the particular month in which she died. In the whole hospital there were 90 staphylococcal infections of all kinds; 75 were penicillin-resistant and 44 were resistant to penicillin, tetracycline, and in most cases streptomycin also. The number of admissions to the hospital during the month was 980, so the incidence of multiply resistant staphylococcal infection in the hospital for that month was approximately 4% or 44 per 1,000. Since then, many measures for the reduction of cross-infection have been taken‡ and the incidence of such infections in the hospital is now less than half what it was.

Nodule Toilet

Dr. M. D. Milne: In view of this experience, is nodule toilet still recognized as a good thing in the management of rheumatoid arthritis, or is it better to retain one's nodules?

Dr. Dixon: I think the answer to that is that this lady's nodules were already ulcerated. We usually feel it is better to have a clean surgical incision, rather than a ragged natural hole, discharging necrotic material from time to time and possibly also acting as a source of metastatic infection.

Professor Bywaters: I think that was the origin of the word "toilet"—to clean it up, in fact. Our practice, whenever one of these nodules gets dangerously near the skin surface, is to advise that the patient have it out.

E.C.G. in Pericarditis

Dr. Dixon: I am still worried in my own mind about these electrocardiograms. I wonder whether any of the cardiologists would like to comment? Dr. Hollman, I think you saw that last tracing. Pericarditis apparently was not present, or at least was not reported, yet the lady turned out to have a pericardium which was in fact a bag full of pus.

Dr. A. Hollman: The incidence of electrocardiographic changes in pericarditis depends on the type of pericarditis. The reason is this: the changes are not due to the pericardial inflammation *per se*; they are due to inflammation or necrosis of the underlying subepicardial muscle itself, and therefore the pericardial process has to dig down a bit to produce changes on the electrocardiogram. That's the first point. And the second one is that of course you don't necessarily expect to see the changes of acute pericarditis at this particular stage. We don't know how long this patient had had a pericardium full of pus, and the cardiograms (Fig. 6) were quite clearly compatible with subacute or chronic pericarditis, since they showed T wave inversion over the left ventricle and I interpret them as being due to this. But since the T inversion is non-specific, naturally one could not distinguish it from T inversion due to ischaemia or any other cause. As a matter of fact I think one of the last tracings did show a little S-T

* Cruickshank, B., *Ann. rheum. Dis.*, 1954, **13**, 136.
† Collins, D. H., *The Pathology of Articular and Spinal Diseases*, 1949. Arnold, London.

‡ Barber, M., Csillag, A., and Medway, A. J., *Brit. med. J.* 1958, **2**, 1377.

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elevation, but I don't think that is a point that should concern us. It was not probably at that stage acute pericarditis and therefore we would not expect to see S-T elevation.

Professor BYWATERS: I wonder perhaps, in view of the considerable observer error and observer interpretation differences which people have recently shown to occur with electrocardiograms, if there are any other cardiologists who would like to comment on it?

Dr. J. P. SHILLINGFORD: I think under the circumstances I fully agree. As the pericarditis becomes chronic, the changes in the electrocardiogram are not so clear cut, and in this case would be compatible with either ischaemia or chronic pericarditis. In fact I agree wholeheartedly with Dr. Hollman, and I shouldn't have said there was any observer error here at all.

Professor BYWATERS: I wonder whether Dr. Azzopardi would like to hazard a guess on the duration of the pericardial lesion?

Dr. J. G. AZZOPARDI: I think it would be of the order of about two weeks, judging by the degree of organization that had taken place in the pericardial exudate.

Dr. BARBER: I wonder if Dr. Azzopardi would like to comment on the staphylococcal pericarditis in the absence of any other staphylococcal processes—whether he, or Dr. Doniach, have had any experience of this, as it seems to be rare?

Dr. I. DONIACH: When Professor Bywaters described the unexpected finding of pus in the joints at necropsy in other rheumatoid patients, I remembered seeing other cases in which widespread purulent infection of joints had been clinically silent.

TERMINAL PHYSICAL SIGNS

Dr. SHILLINGFORD: I wonder if I may ask about some of the physical signs found at the time of her terminal illness? Had she any shortness of breath associated with this high venous pressure? Was she able to lie flat? Was there anything particular about the venous pulse which would make one suspect that she might have pericarditis or a pericardial effusion?

Dr. DIXON: I think you have to remember the time sequence here. She was first thought to be in cardiac failure some six weeks before the terminal admission, and at that time the cardiac failure was mild. I don't think we recorded whether she was so breathless that she couldn't lie flat, but I believe that she was not. At the terminal admission she was very ill and only lived 12 hours. The neck veins were by then completely distended up to the angle of the jaws and no special venous wave-form was noted. She was treated as having congestive cardiac failure. I think she must have developed her pericarditis perhaps a week, perhaps two weeks, before she died, as a complication of previously existing congestive cardiac failure. This would fit in with the history, the fact that she developed an exacerbation of shortness of breath about a week before she died, and got pain in the epigastrium, worse on breathing, about this time. It would also fit in with Dr. Azzopardi's comments regarding the degree of organization of the pericardial exudate.

Dr. C. PALLIS: Is there sufficient fibrosis in the myocardium to account for the myocardial failure, if there hadn't been fluid in the pericardium itself? Or do you think that the presence of fluid acted also as a mechanical impediment to filling?

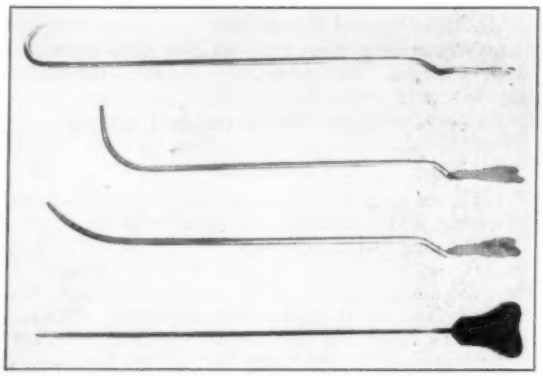
Dr. DONIACH: That part of the heart where the section was taken—the basal portion of the posterior left ventricle—is the part where we do find scarring frequently at necropsy, without necessarily any history of recent heart failure. So I agree with Dr. Dixon that in this case the pericarditis was the main contributory cause of the heart failure.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

New Appliances

A SET OF PROBE-POINTED DIRECTORS

Mr. H. E. LOCKHART-MUMMERY, surgeon, St. Mark's Hospital, London, writes: The standard probe-pointed director has two disadvantages: it is often too big to enter narrow tracks and the groove usually ceases 1 to 2 in. (2.5 to 5 cm.) from the tip. The set of probe-pointed directors illustrated here has been designed primarily for use in rectal surgery, but I believe they may be found useful in the surgery of any fistula or sinus.



The set consists of four directors—one straight, one with a slight curve, one curved to a right-angle, and one curved back like a shallow hook. They are made of hard steel, and, though slim and light, are not malleable; with the different curves available in this set a malleable retractor has not been found necessary. The groove extends along the whole length of the director to within $\frac{1}{8}$ in. (3 mm.) of the tip. The handle is offset to the line of the shaft, which makes for easy handling. I have used these directors for over a year in cases of anal fistula of all types and have found them to be very satisfactory.

They were originally made for me by Messrs. Heaton Grogan Co., Ltd., 21, Bowling Green Lane, London, E.C.1, but they are available through all major surgical instrument firms.

The Victorian State Government is considering raising the marriage age for girls to 16 years and for boys to 18. The present minimum ages in Victoria and New South Wales are 12 years for girls and 14 for boys. The Anglican Archbishop of Sydney, calling on the clergy to urge Federal and State Governments to raise the age limits, said that this was one practical way to reduce the divorce rate. The Victorian Chief Secretary said that new legislation was already being considered. The Parliamentary Statute Law committee had recommended raising the ages to 16 and 18. (*Radio Australia News*, September 22.)

Drug Treatment of Disease

DRUG TREATMENT OF ECZEMA

BY

S. T. ANNING, M.A., M.D., F.R.C.P.

Dermatologist, The General Infirmary, Leeds

Eczema, or eczematous dermatitis, is an eruption of the skin characterized primarily by pinhead-sized macules, papules, and vesicles and accompanied by intense itching or burning. Erythema may be a prominent feature, or oedema (as when the eyelids are affected) or blisters, as in the thick skin of the palms and soles in pompholyx. In the acute phase "weeping," or the exudation of serum from burst vesicles, is usual, and secondary infection may occur, with pustules and crusting. Excoriations are commonly seen, and in the more chronic phase there is scaling, and, as a result of friction, the skin becomes thickened or lichenified.

Eczematous dermatitis is a reaction of the skin to external or internal factors, usually to both. External factors may be primary irritant substances (e.g., acids, alkalis, turpentine, etc.) or sensitizing agents (allergens). It has been said that almost anything under the sun, and the sun itself, may provoke allergic sensitization in the skin. Certain drugs used in medical practice—the sulphonamides, penicillin, streptomycin, chloramphenicol, the antihistamine compounds, and other local anaesthetics such as the benzocaine group—if brought into contact with the epidermis for more than a few days are particularly apt to cause sensitization.

Internal or constitutional factors include heredity (for this reaction is often familial), age (for it is more common during infancy, puberty, the menopause, and senescence), and deterioration in health, both physical and mental. Emotional upsets are well recognized as a precipitating cause in some patients.

Eczematous dermatitis is therefore a general medical problem in which the patient as a whole must be considered as well as his family, his environment, and his past history. Unless the internal and external factors responsible for the condition are carefully analysed and dealt with, the mere application of various medicaments to the skin and the exhibition of drugs internally are likely to achieve little.

TOPICAL APPLICATIONS

Certain principles should guide the choice of topical applications. As the affected skin requires to be soothed and protected, bland, non-irritant substances should be used. In deciding whether to employ a lotion, a paste (containing a large proportion of solid matter), an ointment (whether greasy or not), a paint or liniment, the individual patient must be considered—his type of skin, the situation affected, and the phase of the eczema. Some patients are intolerant of grease on their skins. For the scalp or other hairy parts ointments containing emulsifying bases should be employed, as these can readily be washed out. Acute eczema must be treated gently.

No substances notorious as sensitizing agents should be applied to the skin. For this reason local anaesthetic and antihistamine creams (which are also local anaesthetics), though they relieve itching for a time, should never be used. Similarly, there is no justification for the topical application of penicillin, chloramphenicol, streptomycin, or the sulphonamides. If their administration is indicated, they can be given internally. The possibility must be borne in mind of cross-sensitization, in which sensitization to one substance may induce sensitization to a number of other chemically related compounds. For instance, sensitization to sulphonamides may result in sensitization to aniline dyes—for example, gentian violet, acriflavine—and to other substances such as benzocaine and promethazine hydrochloride ("phenergan").

Lotions

Eczema in the acute weeping phase is best treated with watery lotions, of which calamine lotion is the best known. The *B.P.* lotion contains bentonite and phenol (about 0.42% w/v). Phenol, though an antipruritic, is an irritant, and in acute eczema the following lotion is likely to be more soothing:

Calamine	40 gr. (2.6 g.)
Zinc oxide	40 gr. (2.6 g.)
Glycerin	30 min. (1.7 ml.)
Aq. calcis	to 1 oz. (28 ml.)

On no account should one of the popular calamine lotions containing an antihistamine drug be prescribed.

Another useful and soothing lotion for acute eczema is:

Zinc oxide Glycerin Talcum Aq. calcis	Equal parts to 1 oz. (28 ml.)

These lotions should not be used as wet dressings but applied thinly with a brush or a pledget of cotton-wool and allowed to dry before covering with "tube gauze" or bandages. There should be a thin film of dry lotion over the area, and more should be applied only to make good deficiences in this film. Thick plaques of dried lotion cause discomfort, especially on mobile areas such as the face and over the flexures.

When acute moist eczema shows evidence of secondary infection, the part may be soaked in a tepid solution of potassium permanganate (1 in 8,000) for ten minutes several times a day, or, if this is impracticable, it may gently be dabbed on. The patient with extensive eczema benefits from lying in a bath of this solution for a quarter of an hour once a day. The bath becomes stained and difficult to clean, but photographic sodium thiosulphate ("hypo") solution is effective for this purpose.

Silver nitrate (1–2%) or gentian violet (1%) in water is also helpful for acute infected eczema. Gentian violet is messy, but, like silver nitrate, tans the raw surface and is comforting. Rarely does the tanning cause sealing-up of organisms, with resulting lymphangitis, but this complication responds rapidly to oral sulphonamide. The use of steroid lotions is discussed later.

An oily lotion or liniment is useful for less acute eczema, but lot. calamin. oleos. *B.P.C.* is too oily and its contents separate readily. More satisfactory and more soothing is:

Calamine ...	40 gr. (2.6 g.)
Lanolin ...	40 gr. (2.6 g.)
Ol. arachis ...	Equal parts to 1 oz. (28 ml.)
Aq. calcis ...	

Pastes

Pastes differ from ointments in that they contain a large proportion of solid matter in the form of finely dispersed powder in a greasy base. Lassar's paste (past. zinc. oxid. et acid. salicyl.), probably the most beneficial local application we have, contains 50% bland powder in soft paraffin (optimum melting-point 46° C.). It should not be spread thickly with a knife on to linen or lint and applied to the skin unless the area is very moist, but with the finger-tips spread gently and thinly until a film covers the area. Although it is stiff it can be applied readily in this way without warming, and forms a soothing, protective covering which allows the skin to cool and perspire normally and which absorbs secretions. Often a dressing is not required when Lassar's paste is used in this way. More paste should only be applied to make good deficiencies in the film, which should not be removed before re-dressing.

If a softer paste is indicated, Lassar's paste may be mixed with an equal quantity of soft paraffin or emulsifying ointment *B.P.* A number of substances may be added to Lassar's paste—gentian violet ½%, or phenoxyethanol 2%, or ammoniated mercury 2% as antiseptics, and coal tar 2–6%, or ichthammol 2%, or podophyllin resin 0.1% as antipruritics. Tar and podophyllin should be applied only in chronic eczema.

Titanium dioxide paste *B.N.F.* is useful for exudative eczema, and it may be mixed with an equal quantity of emulsifying ointment to make a softer application.

Ointments and Creams

Ointments have greasy bases of which soft paraffin, castor oil, and wool fat are common examples. Creams are different in that they contain, in addition to greasy materials, emulsifying agents and water. The emulsion may be a mixture of oil in water or vice versa. Creams are indicated when the skin is inflamed, for the evaporation of water has a cooling effect, when there is an exudate, and when hairy skin requires treatment. Ointments, on the other hand, are useful for dry, hyperkeratotic, scaling, and fissured skin. With such conditions zinc and castor oil ointment *B.P.* is helpful.

A variety of active agents including coal tar, steroids, and antibiotics are added to ointments and creams.

Coal tar has already been mentioned as an antipruritic and is a valuable preparation for chronic eczema, in which, in addition to the relief of itching, it reduces lichenification. Even when used for long periods the risk of carcinoma is negligible. Comparison with experiments in mice is not valid. Kinmont (1957) showed that certain fractions of coal tar are more effective than prepared coal tar *B.P.* in the treatment of eczema, and ointments containing them are available.

It is convenient here to mention other ways in which coal tar may be used in the treatment of chronic eczema. Crude coal tar may be painted over the affected area and drying may be hastened by the use of an electric hair-dryer. It remains for a week or more as a protective, antipruritic covering, though in places may have to be replaced daily. It can be removed by the application of Lassar's paste. Its colour is a disadvantage and it is useful only on the limbs and trunk. An alternative for the limbs is one of the proprietary linen bandages impregnated with tar (e.g., "coltapaste," "dalzoband No. 6").

Steroid preparations, as ointments, creams, and lotions, are valuable in the treatment of eczema, but their effect is temporary. Cost limits their use, and if large areas of skin are affected they are contraindicated for this reason. Steroid preparations, being cosmetically pleasant, are especially useful for eczema of the head and neck, and for eczema of the ano-genital region. It must not be thought that steroids are essential in the treatment of eczema; bland lotions and pastes are often preferable.

Steroid applications sometimes irritate the skin, and usually the base is responsible. The patient may be allergic to the base, or, when the latter is greasy, merely intolerant of oily materials.

The great variety of steroid ointments and lotions on the market to-day makes the choice difficult for the prescriber. He must decide whether to use an ointment, and if so whether greasy or otherwise, or a lotion. For moist, exudative areas a non-greasy preparation or a lotion is best, but for dry eczema, especially with fissuring, a greasy ointment is preferable. A lotion is often more suitable for the flexures.

There is no need to use hydrocortisone preparations in a strength greater than 1%, and often 0.5% is sufficient. Prednisolone is more effective and 0.25% or less is enough. There is little evidence that glycyrrhetinic acid has a cortisone-like action.

The combination of steroids and antibiotics or antiseptics is usually unnecessary and may be disadvantageous. Often it means that a sensitizing agent or an irritant substance is introduced to no purpose. The belief that the treatment of eczema with steroids may encourage local infection is unsound. It is only when eczema is grossly infected, even impetiginized, that the combination is useful, except, occasionally, for eczema of the external auditory meatus (otitis externa). When infection is a prominent feature, it is best treated by antibiotics given internally.

If *antibiotic and antiseptic* ointments and creams are indicated, it is essential that neither irritant substances nor those apt to provoke allergic sensitization should be used. It is wise to employ antibiotics which are never prescribed for internal treatment, and for this reason ointments containing neomycin and gramicidin or bacitracin are popular. Useful antiseptic ointments are those which contain chlorquinaldol ("steroxin"), iodochlorhydroxyquinoline ("vioform"), chlorhydroxyquinoline ("quinolor"), and phenoxyethanol ("phenoxetol").

INTERNAL MEDICATION

Sedative drugs are usually required for the tense, anxious, irritable patient with eczema, but large doses are unnecessary. Amylobarbitone ¼ gr. (16 mg.) two or three times a day is helpful and is less depressing than phenobarbitone in the same dosage. Potassium bromide is a valuable sedative and harmless if not prescribed for the elderly and not taken for more than a few weeks at a time. A dose of 7 gr. (450 mg.) twice or thrice daily is sufficient. Bromide eruptions are rare but must be watched for.

Antihistamine drugs play no part in treatment except as sedatives, because histamine is not released in the eczema reaction. In children as well as adults they are useful as hypnotics and help to reduce nocturnal irritation. They are, of course, contraindicated when the patient is allergic to certain antihistamines or chemically related compounds. The best antihistamines for use as hypnotics are diphenhydramine hydrochloride ("benadryl") 10–50 mg. and promethazine hydrochloride ("phenergan") 25–50 mg. given at night in capsules, tablets, or (for children) in an elixir.

Tranquillizing drugs have already been considered in this series of articles by Vogt (1958) and Sargant (1958). In this group of drugs hydroxyzine hydrochloride ("atarax"), which is also an antihistamine, seems to be the most effective in relieving the itchy patient, but it is expensive. Nevertheless, a small dose (10 mg. twice daily) is sufficient. Trimeprazine (10 mg. twice daily) is a good antipruritic.

Steroid drugs are rarely indicated for the internal treatment of eczema, and their chief use is in acute eczematous dermatitis provoked by sensitization to an allergen which can be identified and removed. Prednisone 5 mg. or triamcinolone 4 mg. or methyl prednisolone 4 mg. may be given four times a day for the first few days, and the dosage reduced gradually to one dose a day by the end of a further week, when treatment can usually be stopped. It is unsatisfactory to use these powerful and effective drugs for eczematous dermatitis of any type until a full assessment of the condition has been made, for the effects are suppressed without treatment of the cause.

Antibiotic drugs and sulphonamides, as has been indicated, are useful when eczema is secondarily infected, and they are better given internally than locally. *Staphylococcus aureus* is the most important organism to be dealt with, and sulphonamide for a few days is sufficient—for example, sulphasomidine 0.5 g. each morning.

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HUMAN CHROMOSOMAL ABNORMALITIES

CONFERENCE AT KING'S COLLEGE HOSPITAL

[FROM A SPECIAL CORRESPONDENT]

A conference on human chromosomal abnormalities was held at King's College Hospital Medical School on September 18 and 19. In many ways this was a sequel to the symposium on nuclear sex held at King's two years ago. At that time it was realized that many of the problems connected with nuclear sex would be solved once satisfactory techniques for examining human chromosomes had been evolved, and it was forecast that that would be in the near future. Many of the technical difficulties have now been overcome. There have been some notable advances, principally in this country and Western Europe, and the conference brought together most of those who have contributed to this work.

Abnormal Sex Chromosomes

By examining cells in mitosis from *in vitro* cultures of bone-marrow and skin it has already been demonstrated that three conditions have chromosomal patterns differing from the normal 46 chromosomes with XX in the female and XY in the male. In two of the disorders the sex chromosomes are at fault. Klinefelter's syndrome is characterized by 47 chromosomes, there being three sex chromosomes, XXY; in Turner's syndrome the majority of cases are "chromatin negative," and these have only 45 chromosomes, the Y being absent, giving an XO sex-chromosome pattern. The other chromosomal abnormality previously described involved the non-sex chromosomes or autosomes. In mongolism there are again 47 chromosomes, the extra autosome being one of the smallest.

These chromosomal abnormalities were discussed at length at the symposium by various speakers. Dr. C. E. FORD (Harwell), who developed the marrow-culture technique of chromosomal analysis, considered that some cases of Turner's syndrome might be "mosaics" showing two different chromosomal patterns in the marrow cells, some cells being XX with 46 chromosomes and the others XO with 45 chromosomes. There was much debate on this point, especially concerning the relationship with a previously described mosaic condition of sex-chromatin in the skin in a case of Turner's syndrome. Dr. Ford thought that the examination for colour-blindness of each eye separately in cases of Turner's syndrome might detect differences which would support the mosaic theory.

Colour-blindness Studies

Three speakers, Professor H. NOWAKOWSKI (Hamburg), Dr. J. S. S. STEWART (Dundee), and Dr. P. E. POLANI (London), described the results of colour-blindness studies in Turner's and Klinefelter's syndromes, from which it was possible to infer the mechanism of development of the chromosomal abnormalities. It appears that in Turner's syndrome no sex chromosome is inherited from the father and the single X comes from the mother, the supposition being that in spermatogenesis non-disjunction occurs during one of the meiotic divisions, so that XY gives rise not to one X and one Y spermatozoon, but to an XY and an O spermatozoon. Conversely, in Klinefelter's syndrome the defect is probably maternal, due to non-disjunction occurring in oogenesis so that XX and O ova are produced, and an XX ovum is fertilized by a Y spermatozoon, giving an XXY zygote. The speakers stressed the importance of further detailed studies of colour-blindness in patients with these disorders and in their relatives.

Miss PATRICIA JACOBS (Edinburgh) described a third type of abnormality of the sex chromosomes in a patient with secondary amenorrhoea and underdeveloped external genitalia, uterus, and vagina. The cells were characterized by the presence of 47 chromosomes and XXX sex chromosomes. This chromosomal pattern is analogous to the "super female" found in *Drosophila*. Some of the oral mucosal cells (and perhaps also some of the neutrophils) showed two sex-chromatin bodies, which should help in finding further cases by ordinary nuclear-sexing methods.

An abnormal sex-chromosome pattern has been postulated as the basis of the testicular feminization syndrome, but Dr. BERNARD LENNOX (Glasgow) showed that in cases he had studied the chromosome pattern was of normal male type—that is, 46/XY.

Abnormalities of the Autosomal Chromosomes

Dr. L. LEJEUNE (Paris) described the findings in a condition other than mongolism which showed changes in the autosomal chromosomes. In a child with polydyspondylism showing multiple bony abnormalities of the skull and spine and with low intelligence there were only 45 chromosomes. One of the smaller chromosomes was not seen perhaps because it had become attached to another chromosome.

Professor L. S. PENROSE, F.R.S. (London), demonstrated the correlation between increasing maternal age and the incidence of mongolism, and suggested that the same might occur in Turner's syndrome and Klinefelter's syndrome, but to prove this detailed data on more cases were needed.

Neutrophil Drumsticks

Dr. W. M. DAVIDSON (London) compared the sex-chromatin bodies in tissue cells and neutrophils, and discussed their relationship to the sex chromosomes. He suggested that an explanation for the position of the sex-chromatin mass at the periphery of the nucleus in many tissue cells, and its extrusion as a drumstick in the polymorphonuclear leucocyte, might indicate that it ceases to have any function after mitosis. Dr. URSULA MITTWOCH (London) considered the causes of variation in frequency of drumsticks in neutrophils and gave the results of counts in mongolism and Klinefelter's syndrome. She thought the low frequency in Klinefelter's syndrome was related to a shift to the left in the Arneth lobe-count, but other speakers did not support this.

Dr. M. FRACCARO (Uppsala) reviewed the long-term cultivation of cells *in vitro* and indicated the sort of condition that might repay investigation for chromosomal abnormality. Dr. D. G. HARNDEN (Harwell) reviewed the considerable number of conditions that had been studied already both by himself and by others, particularly those familial and congenital disorders of development which involved more than one system. Of equal importance to the finding of abnormalities is the reporting of negative results, and he was able to report normal chromosome-patterns in anencephaly, microcephaly, osteogenesis imperfecta, chondrodystrophy, neurofibromatosis, epiloia, retinitis pigmentosa, Laurence–Moon–Biedl syndrome, amaurotic family idiocy, and schizophrenia.

Dr. H. P. KLINGER (Basle) described an interesting finding in a human amnion. In one area there was an increased amount of desoxyribonucleic acid and sex chromatin in the cell nuclei, which he thought might represent an early tumour of amnion. Dr. N. B. ATKIN (Northwood) reviewed his work on chromosomal studies in human tumours, and gave evidence for the reorganization of the chromosomal material in cells of mammary carcinoma, and Dr. W. M. COURT BROWN (Edinburgh) showed a similar phenomenon in marrow cultures from cases of acute leukaemia in adults.

Technical Methods

In his concluding address Dr. C. E. FORD compared the bone-marrow and tissue-culture methods of preparing human chromosomes. The marrow method gave quick results, but was more difficult, whereas the skin cultures took two or three weeks and were easier, but unwanted artifacts could arise in the cultures. In the autosomal abnormalities found in mongolism and polydyspondylism it was one of the smallest chromosomes which was involved; probably changes involving the medium- and large-sized chromosomes were lethal. They might be found in material after spontaneous abortions. The X chromosome (a medium-sized chromosome) obviously differed in this respect in that variations in number from one to three could be tolerated. Although there was at present no direct evidence implicating changes in the chromosomes as a cause of neoplasia, Dr. Ford thought that genetic change in its widest sense was a part of neoplastic progression. He anticipated considerable progress in this field.

The New Health Trust has made a contribution of £700 to the Queen Elizabeth Hospital for Children, London, towards the study of hypercholesterolaemia in children. The research is under the general direction of Dr. ALEXANDER RUSSELL, of the Queen Elizabeth Hospital, and Dr. LEONARD SINCLAIR, of Guy's Hospital, has been appointed to a New Health Trust Fellowship for a period of two years on a part-time basis. The New Health Trust was created in 1951 to further the objectives of the New Health Society, founded in 1925 by Sir WILLIAM ARBUTHNOT LANE. The Society concerns itself with preventive medicine and health education.

SEVENTH ANNUAL ANTIBIOTICS SYMPOSIUM

[FROM A SPECIAL CORRESPONDENT]

Six years ago this journal contained a report* of the First Antibiotics Symposium held in Washington, D.C. This symposium has become an annual event, the proceedings being published in an increasingly ponderous volume entitled *Antibiotics Annual*. The Seventh Symposium was held on November 4–6 last, when it was revealed that 278 papers had been submitted; but many of these were only "read by title," and, in order to provide for the rest, two simultaneous sessions were necessary (on one occasion three), and the times allotted for delivery were 12, 10, or 8 minutes The organizers, among whom the leading figure is Dr. HENRY WELCH, of the Food and Drug Administration, are to be congratulated on the continued popularity of this meeting, despite much criticism on the quality of many of the papers submitted. It remains the principal forum for discussion of this important branch of therapeutics—although what goes on in the lobbies is of more interest than discussion in the meetings themselves, for which there is too little time—and it has become a medium for the first presentation of work on which the introduction of a new antibiotic is based.

Challenge to the Clinical Investigator

A few distinguished contributors were given the opportunity of speaking on general subjects. Dr. MAXWELL FINLAND, entrusted with "The Challenge of New Drugs to the Clinical Investigator," had some hard things to say about "saturation and brain-washing methods" in sales promotion, and emphasized that it is one of the more unpleasant duties of the investigator to ensure the "elimination of the second-rate." He also deplored the fact that the number of those so situated and qualified as to be able to conduct an adequate clinical trial are far too few: little short of Government action could ensure that both time and facilities were available to the right type of investigator. He might perhaps have added that comparative trials which will distinguish between the merits of some closely similar antibiotics and other chemotherapeutics now available could well yield an equivocal answer even under the best conditions.

Dr. R. J. DUBOS, whose discovery of gramicidin was so important a link in the chain leading to present-day antibiotic therapy, reviewed his earlier work in this field, and discussed reasons for the frequent failure of antibiotics in chronic infections, which is in so strong a contrast with their success in acute. In a focus of chronic infection the low *p*H and the presence of acidic mucopolysaccharides, nucleic acids, and other tissue breakdown products may all contribute to neutralizing the activity of an antibacterial drug. None of these is taken into any account in the screening procedures at present applied to new antibiotics, and Dubos suggested that these methods should be varied to select substances active under such conditions.

Although many new names of antibiotics appeared in the programme—either entirely new or variants of others already known—interest centred chiefly on the three following.

A New Penicillin

Reference was made in the *Journal* for November 7 (p. 940) to the launching of a new penicillin by way of a public press conference with no prior announcement to the medical profession. A group of five papers at this meeting constituted the first medical publication of what is hitherto known about this substance (which was here referred to as

* *Brit. med. J.*, 1953, **2**, 1043.

potassium (α-phenoxyethyl) penicillin). As has already been made clear, its main advantage is that of better absorption: the peak levels attained in the blood were variously reported as from twice those given by peniciilin V to (apparently) about 50% higher. One series of blood estimations showed similar curves after oral and intramuscular administration, although the peak given by the latter was of course earlier: this finding suggests that absorption from the alimentary tract is complete, although the fact that as little as 30% of the dose may be recovered from the urine seems against this. Excretion is at the same rate as for penicillin V: there is thus no more-prolonged effect.

The new compound is less active *in vitro* than penicillins G and V against streptococci, but is claimed to possess equal therapeutic efficacy in streptococcal and pneumococcal infection in mice. It is claimed to have a superior action to that of other penicillins against mouse staphylococcal infection, but no details of this finding were given. Very varying findings were reported about the sensitivity of penicillinase-forming staphylococci: some strains are apparently much more sensitive *in vitro* than to other penicillins, and the basis of this is *slower* inactivation of the new penicillin by the penicillinases of both staphylococci and *B. cereus*. The only detail of this finding given was that under unspecified conditions 64% was inactivated when the inactivation of penicillin G (? V) was total. On the other hand, infection in mice by penicillinase-forming staphylococci was not controlled. This is a confusing picture, which may or may not indicate some superiority of therapeutic action in the most troublesome of all bacterial infections. Obviously more work on this needs to be done, and it is most unsatisfactory that what has been done should not yet be in print when the product has already been launched commercially. A common feeling was that judgment on the merits of this product should be suspended until more information is available.

New Tetracyclines

It is strange, as one speaker remarked, that progress in modifying the tetracycline molecule is being achieved by detaching fragments of it, when the more usual line of advance is by additions. Tetracycline itself was arrived at by subtracting a chlorine atom from chlortetracycline: removing a methyl group from it yields demethylchlortetracycline ("declomycin" in the U.S.A., "ledermycin" in Europe), the subject of the largest group of papers, totalling 13, on any single antibiotic. The findings of leading investigators about this antibiotic have already been published: it has a high stability, in contrast to the extreme instability of chlortetracycline; its activity against all species (staphylococci, streptococci, and *B. cereus*) used in assay procedures exceeds that of tetracycline, and, most important of all, it not only attains slightly higher initial levels in the blood than tetracycline, but sustains them longer: its "half-life" was given as 12.7 hours, that of tetracycline being 8.5. Slower renal excretion, possibly combined with greater stability, accounts for this. These properties should enable it to be given in smaller doses than tetracycline and at longer intervals. There was some disagreement about whether concentrations of this antibiotic in the blood should be expressed in absolute values or as tetracycline equivalents, a technical matter but with an important interpretative bearing which will have to be settled. New observations were reported on the activity of the antibiotic against a wide range of bacteria: there was no instance of an activity less than that of tetracycline, and one author gave 69% as the proportion of various organisms against which activity was greater. There were also reports of successful clinical use, including one from Mexico on the treatment of brucellosis: nine cases recovered after one course with no relapse.

A small group of papers dealt with pyrrolidinomethyl tetracycline, an injectable form of tetracycline which has been developed in Germany. The levels attained with it in the blood and other body fluids and various tissues are much higher than those produced by the same dose of tetracycline orally; indeed, the differences are so great that absorption of oral tetracycline must be very poor in the animals used. There was little information about therapeutic effect, but brucella infection in mice was reported to be more susceptible to this compound than to tetracycline.

Colistin

This antibiotic, described in Japan in 1950, and developed in the U.S.A., is now available as sodium colistinmethanesulphonate. It is a cyclic polypeptide, having close affinities with the polymyxins, particularly E, but differing from them in having apparently no renal toxicity. One author produced a formidable table of numbers of patients exhibiting toxic effects, including albuminuria and casts, from polymyxin, whereas the number suffering any of these during colistin administration was nil. It is highly active only against Gram-negative organisms, not including *Proteus*, and bactericidal even in the lowest concentration inhibiting growth: resistance to it does not develop easily, but the extent to which this is possible is not clear. Administration can be either oral, mainly for an effect in the bowel, since little is absorbed, or intramuscular: it is excreted in the urine, where the concentration attained is about 20 times that in the blood. Both routes of administration have been tried, the oral being rather more effective, for acute intestinal infections in children: specific *E. coli* infections respond best, *Salmonella* fairly well, and *Shigella* poorly. This antibiotic could clearly be of great value in treating serious infections by organisms such as *Ps. pyocyanea*, and its apparent freedom from renal toxicity gives it a great advantage.

It is interesting that of these three clinically important innovations two are merely variants of established antibiotics. So far as your correspondent was able to ascertain —his limitation being an incapacity to be in two places at once—none of the other new names refers to a substance of yet established clinical usefulness.

OCCLUSIVE ARTERIAL DISEASE

CONFERENCE AT ROYAL COLLEGE OF PHYSICIANS

[FROM A SPECIAL CORRESPONDENT]

The President, Sir ROBERT PLATT, opened the proceedings of a conference at the Royal College of Physicians on November 13 and 14 on "The Pathogenesis and Treatment of Occlusive Arterial Disease." The conference was arranged in four parts: Pathogenesis of Arterial Disease; Cerebral Vascular Disease; Coronary Artery Disease; and Peripheral Vascular Disease.

Pathogenesis

The first part was opened by Professor J. H. DIBLE, who spoke on atheroma particularly in the arteries of the lower limb. The incidence of atheroma was proportional to the size of the artery, the digital arteries showing little or no involvement. With advancing age, intimal thickening occurred, but was not necessarily associated with atheroma. Organization of thrombus in an atheromatous artery did not occur, notably because the internal elastic lamina formed a barrier to the vasa vasorum growing in. The thrombus commonly opened up into a number of small channels lined by endothelium, thus promoting recanalization.

Professor C. V. HARRISON spoke on other occlusive arterial diseases, including giant-cell arteritis, polyarteritis nodosa, and thrombo-angiitis obliterans, and contrasted them with atherosclerosis.

Sir HOWARD FLOREY, F.R.S., then discussed the production of experimental atheroma in different types of animals, pointing out the importance of a diet rich in cholesterol, and the difficulty of reproducing the exact human lesion. Electron microscopical studies showed that the endothelium could take up fat-laden macrophages, which passed through the arterial wall, but no necrosis or thrombosis occurred. An increase in serum cholesterol could be produced in rabbits by a diet lacking certain essential fatty acids, the administration of which would then reduce the cholesterol level. Thus each of certain essential fatty acids might be important in the pathogenesis of atheroma. A naturally occurring form of atheroma in certain types of pigeons had recently been described which was unrelated to diet and sex, indicating the possible importance of genetic factors.

Dr. G. J. POPJAK discussed lipids in relation to atheroma, stressing the relation between increased serum cholesterol and the fatty composition of atheromatous plaques. The metabolism of cholesterol had been studied with tracer isotopes. Cholesterol accumulation in the body could result from an excess of supply over elimination, but the intake of substances which interfere with the absorption of cholesterol would reduce this. Such a substance was sitosterol, which was not itself absorbed. Dr. Popjak reviewed the complex enzymatic reactions involved in the synthesis of cholesterol, and stressed the association between atherosclerosis and the nature of the dietary fat, pointing out that the rate of elimination of cholesterol was increased by taking unsaturated fatty acids. Certain precursors of cholesterol had been investigated for their efficacy in eliminating cholesterol. In addition to the entry of lipids into the arterial wall, it had been suggested that the aortic wall could itself synthesize lipid: the importance of this was not known. Consideration might be given to attempts to reduce the accumulation of cholesterol before serious atherosclerotic lesions developed.

Dr. J. C. F. POOLE and Professor G. PAYLING WRIGHT discussed the formation of artificial thrombi *in vitro*, and thrombosis and vascular occlusion *in vivo*, respectively, and Dr. Poole commented on the difference between thrombus *in vivo* and clot *in vitro*, and described his method for producing *in vitro* thrombus similar to that occurring naturally in the body.

Cerebral Vascular Disease

With Dr. J. ST. C. ELKINGTON in the chair, Dr. E. C. HUTCHINSON opened the session on cerebral vascular disease and spoke on basilar-carotid artery syndromes. In the majority of 100 patients studied clinically and by a special injection technique at necropsy, occlusion of the carotid or vertebral arteries outside the skull was responsible for infarction of the brain. Clinically the association of recurrent transient episodes of hemiparesis, with monocular visual loss, and a murmur over the carotid artery was virtually diagnostic of carotid occlusion. But the picture was variable; it might be slowly progressive, and mental changes might predominate, so that angiography was often essential for diagnosis. With vertebral artery occlusion there might be ocular palsies, dysarthria, and pyramidal lesions. Arthritis of the neurocentral joint was an occasional cause. Dr. Hutchinson concluded by saying that surgery offered the best hope of relieving these syndromes.

Dr. J. W. D. BULL reviewed the available radiological techniques for investigating the acute stroke. Simple radiography should always be performed, but cerebral angiography was often needed, although a comparatively crude method with definite limitations. Thus of 80 patients with acute stroke examined in this way 44 had normal angiograms, and experience had shown that a normal angiogram and even encephalogram might not exclude an intracerebral haematoma. Narrowing and irregularity of arteries were often seen on angiograms, but this did not necessarily correlate with the presence of arterial occlusion.

Mr. WYLIE MCKISSOCK discussed the results of intracerebral surgery in primary intracerebral haemorrhage. Approximately 30% of his patients had died during the 10-year period following operation, but 60% of the survivors had little or no disability. Age under 70 years was no bar to surgery. The site of the haemorrhage was important: deep capsular haemorrhage involving the ventricles or basal ganglia carried nearly a 100% mortality. Hypertension was important only in so far as it tended to cause such haemorrhage. The level of consciousness at the time of operation was also critical, the mortality being 100% if the patient was in a coma, but only 23% if mentally alert. Mr. McKissock pointed out that the results of surgery could not be compared with those of conservative treatment until matched series of patients treated in both ways became available.

Professor C. G. ROB spoke on the surgery of the internal carotid and vertebral arteries in the neck. The results of thrombo-endarterectomy were very much better if the vessel was stenosed rather than completely occluded, when thrombosis tended to spread up into the intracerebral portion of the vessel, where it became inaccessible. Only 4 of 18 patients operated on for occlusion of the internal carotid artery had had a satisfactory blood-flow restored, and these were very early cases. Early diagnosis of stenosis was therefore vital. The importance of recognizing the significance of the association of minor neurological syndromes, even if followed by full recovery, with murmur over the carotid or vertebral arteries in the neck could not be overstated.

Dr. D. A. SHAW, discussing the supportive treatment of the patient with acute stroke, said that patients with non-embolic cerebral vascular accidents treated with anticoagulants within 72 hours of the episode did no better than patients treated without.

Dr. J. MARSHALL dealt with the long-term management of cerebral vascular disease. He stressed the importance of controlled trials in the assessment of treatment, and said that the position of hypotensive therapy was not clear. They had ceased using anticoagulants because there was an appreciably higher incidence of haemorrhagic complications and fatal cerebrovascular accidents in those treated compared with those untreated. Dr. Marshall advised against the indiscriminate use of anticoagulants in cerebral vascular disease, emphasizing that the differential diagnosis between haemorrhage and thrombosis could not always be made. This did not mean that there would never be any place for anticoagulants, but if used at all they should be restricted to recurrent brain-stem lesions. In discussion, Mr. WYLIE MCKISSOCK also stressed the difficulty of clinical diagnosis between haemorrhage and thrombosis, and advised a clinical definition of "acute cerebral vascular accident" pending further special investigation, which should be undertaken in patients who were alert but had extensive neurological signs.

Coronary Artery Disease

On Saturday, with Dr. EVAN BEDFORD in the chair, Professor J. N. MORRIS opened the session on coronary artery disease with a paper on epidemiology and diet. Atheroma was not the same as occlusive atherosclerosis, but the association between high blood-pressure, high blood lipids, and atherogenesis was most important, and the risks of ischaemic coronary artery disease were much increased in subjects with hypertension and hypercholesterolaemia. Populations which consumed mainly vegetable fats suffered less coronary artery disease than those which lived principally on animal fats, but international statistics were fallible and controlled field surveys were required on a national basis to determine the exact place played by diet in the pathogenesis of coronary artery disease.

Dr. M. F. OLIVER then discussed the sex differences in the incidence of coronary artery disease and in blood lipid patterns. Coronary artery disease was much commoner in

men than in premenopausal women, but the difference disappeared after the menopause. Bilateral oophorectomy performed before the menopause was associated with an increase in the frequency of the disease, which suggested that female sex hormones might confer some immunity. The blood lipids followed the same pattern, the cholesterol falling at the time of ovulation and rising after the menopause. Oddly enough, the lipid patterns during pregnancy were closely similar to those in men suffering from coronary artery disease, even though oestrogenic activity was high at this time. There was evidence to suggest that coronary artery disease was commoner in women with large families than in those with few children.

Dr. A. G. LEATHAM illustrated his method of coronary arteriography in dogs with outstanding ciné-angiocardiographic films. Dr. T. CRAWFORD described some aspects of the pathology of coronary occlusion, stressing the frequency of multiple arterial involvement and of multiple thromboses in the same artery. He was sceptical of the importance of subintimal haemorrhage as a factor in precipitating occlusion.

Professor R. S. PILCHER described experimental surgical treatment. Myocardial implantation of the internal mammary artery in dogs would produce a small flow of blood into the myocardium, and the operation protected against death from coronary artery ligation, but only after an interval of several weeks. Better methods, such as coronary endarterectomy, or arterial grafting, were required, and coronary arteriography would be an important preliminary investigation to such surgical endeavours.

Dr. A. RAE GILCHRIST opened the discussion on anticoagulant therapy, reviewing the reduction in mortality and in recurrent thrombo-embolic episodes in patients with acute myocardial infarction treated with anticoagulants. He thought that the results of the use of anticoagulants in acute coronary insufficiency were encouraging, and that there was a good case for using anticoagulants in patients with angina of effort, in an attempt to prevent infarction. Dr. ROSEMARY BIGGS said that the problems involved in the widespread use of long-term anticoagulant therapy would be considerable because of the difficulty of arranging simple but sufficiently reliable prothrombin tests, and also from the viewpoint of organizing clinical and laboratory facilities for control on a very large scale.

Professor J. MCMICHAEL, F.R.S., drew attention to the similarity of the prognosis after a single acute attack of cardiac infarction in groups treated with anticoagulants and those not so treated. He also drew attention to the inconsistencies between the results of certain trials of anticoagulants, and doubted whether the evidence of benefit was sufficiently clear to warrant the inconveniences and dangers of protracted therapy. He concluded by suggesting that long-term anticoagulant therapy for coronary artery disease should be abandoned. In the discussion, Dr. BEDFORD said that he used anticoagulants in selected cases of acute cardiac infarction, and had an open mind about their long-term use.

Peripheral Vascular Disease

The final session, on peripheral vascular disease, under the chairmanship of Sir GEORGE PICKERING, was opened by Dr. E. L. MCDONALD, who emphasized the value of detecting at the bedside changes in the peripheral pulses on exercise and of tonoscillography. Professor H. BANCROFT spoke on the role of the sympathetic nervous system. It exerted negligible control over blood-flow to muscle, its control being limited to blood-flow to the skin.

Dr. W. G. OAKLEY spoke on peripheral vascular disease in diabetes, and stressed the importance of neuropathic lesions of the extremities in contributing to necrosis of tissue and gangrene. Amputation was often required and should not be delayed too long, but sympathectomy was sometimes of value in relieving pain in an ischaemic limb.

(Continued at foot of next column)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Polyvinyl pyrrolidone

Large quantities of polyvinyl pyrrolidone have been given intravenously without obvious ill-effect as a substitute for plasma. It is well established that the smaller molecules are excreted by the kidney, while larger molecules are stored in reticulo-endothelial cells indefinitely. The substance is not broken down in the body.

"Periston N" (Farbenfabriken Bayer) consists of polymer molecules small enough to be quickly and almost completely excreted by the kidney. The mean molecular weight is said to be 12,600±2,700, with an upper limit of 40,000. The preparation is intended, to use the makers' phrase, "for the detoxification of blood and tissues."

Polyvinyl pyrrolidone has been shown to possess adsorptive capacity for various substances; it competes with plasma proteins and tissue surfaces for their adsorption. When it leaves the blood-stream in the kidney, the adsorbed substances are removed too. Some striking experiments on the removal of dyes from the tissues of living animals support this explanation, but quite possibly other factors are involved as well.

On the basis of this experimental evidence it seems reasonable that periston N might be useful in the treatment of various toxaemias. German workers claim clinical improvement in diphtheria, tetanus, and dysenteric disorders. Another rational application of periston N is in the treatment of overdosage with drugs—e.g., barbiturates. In principle a separate assessment of the efficacy of periston N is required for each toxic substance.

In considering the use of periston N it is worth remembering that adequate renal function is required for success, and also that there is no reason to suppose that only unwanted substances are selectively removed: drugs, vitamins, or hormones might be removed together with toxins.

N.H.S. Basic Price.—1×100-ml. pack, 13s. 11d., 5×100-ml. pack, 62s. 6d.

(Continued from preceding column)

In bed local pressure on ischaemic tissue should at all costs be avoided.

Dr. J. F. GOODWIN discussed medical treatment. He emphasized the importance of attending to vascular and other disease elsewhere in the body, and of preventing further peripheral arterial disease. Medical treatment of ischaemic limbs was of limited benefit; only the surgeon could provide definitive local treatment, and he should be consulted early, especially in arterial embolism. Protection from embolism in mitral valve disease was most important, and could be afforded to some extent both by initial valvotomy in suitable cases and by long-term anticoagulant therapy.

Mr. G. W. TAYLOR said that the most effective surgical treatment was a direct attack on the thrombosed artery, such as by bypass arterial grafting, and to date the long-term results were encouraging. Sympathectomy was of value in increasing skin blood-flow, and was helpful in patients with early nutritional changes in a limb, but it seldom saved a severely ischaemic limb from amputation, and did not benefit intermittent claudication, which was only relieved by some form of arterial reconstruction.

The President closed the Conference by thanking the speakers and chairmen. The *Proceedings* will be published in full in book form.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Barnet Ventilator

SIR,—Through the medium of the press, both in descriptive articles and in expensive advertisements, and also on television and, I believe, in the newsreels, has been launched to the lay public, as well as to our colleagues, the news of the development of a machine for assisted respiration. I am not complaining of this publicity if it leads to the clearer understanding of the necessity for better machines for lung inflation. What I do not care for is what I consider to be a misleading claim that this apparatus outmodes and makes obsolete the so-called "iron lung." This claim, as many of my colleagues who work with me in the field of prolonged artificial respiration will surely agree, is absolute nonsense.

I can only conclude that those who have allowed such a claim to be broadcast are either ignorant of the value of the modern cabinet respirator (incidentally the pictures which have appeared show a modified pre-war model of the cabinet type) or have allowed their enthusiasm to override their judgment. For instance, I would not like to have to treat an acute and possibly cerebral polio patient, especially a child or infant, with lung inflation by mask or mouthpiece. Nor, as an alternative, would I like to inflict a tracheotomy on a patient in whom the operation might be avoided. But if tracheotomy has to be done and artificial respiration be indefinitely prolonged, this new machine may be an excellent acquisition for our respiratory units. We would acquire it only as an addition to our present equipment, which includes various machines for prolonged or short-term ventilation by intermittent positive-pressure through mask, mouthpiece, dome, or tracheostomy. We know, I think, where these machines have their uses, but we are also in no doubt whatever about the great value of the "iron lung."—I am, etc.,

Western Hospital, London, S.W.6. W. HOWLETT KELLEHER.

Toxic Epidermal Necrolysis

SIR,—I read with great interest Dr. J. V. F. Catto's report of toxic epidermal necrolysis occurring in a 3-year-old child (*Journal*, September 26, p. 544).

Since Dr. Lang and I[1] described what we believe to be the first case of this condition ever recorded, and since the subsequent reports of Lyell[2] and Rook[3] and our further four cases,[4] I have moved from Capetown to Durban, where I am on the staff of the King Edward VIII Hospital, which caters for the Bantu and Indian community of Natal. On my arrival, I found that not only the senior dermatologist, Dr. J. A. L. Leeming, but the entire paediatric, medical, and surgical staffs, and even the medical students, were well acquainted with this condition so admirably named by Dr. Lyell "toxic epidermal necrolysis."

It is by no means uncommonly seen here in all age groups, particularly in very young children, the youngest I have seen being a Zulu baby aged 5 months with no history of drugs whatever. The paediatricians, before they had read the case reports, were very naturally in the habit of endeavouring to obtain a history of scalding and were tempted to accuse the mothers of lying when no such history was forthcoming, so very similar to scalds are the skin lesions. Dr. Catto's remark about the forensic importance of being able to recognize toxic epidermal necrolysis reminds me that the house-physician refused to sign a death certificate when our first patient, the Bantu male, died, so strongly did he suspect that death was in fact due to burns or other unnatural causes—for example, the ministrations of a witch-doctor. It was only the extensive though negative investigations by the police which put his mind at rest on that score. The actual aetiology, however, remains obscure.—I am, etc.,

Durban, S. Africa. JEAN WALKER.

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[3] Rook, A., *Arch. belges Derm.*, 1957, **13**, 391.
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Onset of Rheumatoid Arthritis

SIR,—Many questions have been asked about the onset of rheumatoid arthritis. Up to now the answers have added nothing positive to our knowledge of the cause of the disease. Perhaps this is because the wrong questions have been asked and the facts have not had a chance of disproving the null hypothesis that the onset is not determined by an external factor. As far as I am aware no one has asked the question: "When did your rheumatism start, which year, and which month?" The answers I got from the first 137 patients questioned are reported in the hope that the same question will be asked in other centres, particularly in the southern hemisphere.

Of the 137 patients 111 stated that the onset of their illness was sudden. They had never had rheumatism before. Ninety-three of these patients were able to date the onset to a definite month and year. Of the 18 patients who declared that the onset was sudden but could not date it precisely, 10 said that their illness started in the winter months, three in the summer months, and five that they could not remember what time of year it started. The number of patients of the 93 who could date the onset to a definite month and year are tabulated according to the month of onset:

Winter Months		*Summer Months*	
October	14	April	3
November	11	May	5
December	9	June	2
January	11	July	6
February	13	August	3
March	11	September	5
Total	69	Total	24
Mean per Month	11.5	*Mean per Month*	4

Difference between means 7.5. $P<0.001$ ($t=7.84$).

It is concluded that rheumatoid arthritis starts about three times more frequently in the winter months than in the summer months, and that the epidemiology of the onset of rheumatoid arthritis needs further investigation.—I am, etc.,

Brook General Hospital, London, S.E.18. GEOFFREY E. LOXTON.

Acroparaesthesia in Pregnancy

SIR,—The carpal-tunnel syndrome is known to occur during pregnancy (*Journal*, May 9, p. 1230), and treatments hitherto described have been splinting[1] and oestrogens.[2]

In general practice I saw recently a primigravida in the 34th week of pregnancy with painful nocturnal paraesthesiae of the hands and other definite symptoms of the carpal-tunnel syndrome. There was no overt pre-eclampsia, but her weight gain had been considerable and her facies showed definite mooning. On the assumption that the carpal-tunnel symptoms might be due to increased fluid retention in the area of the wrists, she was given an oral diuretic twice weekly. With the initial dose her 24-hour urine output rose from 1.4 to 3.3 litres and her painful paraesthesiae almost completely disappeared. A return of the previous symptoms followed five days after the drug was withheld, but improvement was consistently maintained while treatment was continued.

The use of an oral diuretic rather than splinting is obviously more convenient for a perhaps busy mother, and seems to constitute a more physiological therapeutic approach.—I am, etc.,

Edinburgh, 8. MOLLIE J. MCCALLUM.

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Marketing of Hormones

SIR,—May I draw attention to the numerous preparations of hormones, which are multiplying in the market, for which wide and diverse claims are made in the treatment of gynaecological disorders?

With increasing frequency one meets cases of post-menopausal bleeding, and menstrual disturbances, particularly around menopausal age, which have been treated "blind" with one or more of these preparations, and which have eventually proved to be due to malignant disease. More rarely secondary amenorrhoea, associated, for example, with diabetes or tuberculosis, has been treated symptomatically with hormones while the underlying disease has been missed.

It is surely an elementary stipulation that no case of menstrual disturbance or abnormal vaginal bleeding should be treated with hormones until an accurate diagnosis has been made. It is seldom that this can be done without biopsy and pathological examination of the material.

Drug firms are doing great harm by their ill-considered advertising of these dangerous temporizers which waste time, when time may mean the difference between life and a miserable death.—I am, etc.,

Omagh, Co. Tyrone. J. H. PATTERSON.

Medical Evidence

SIR,—Dr. R. F. Tredgold's letter on medical evidence (*Journal*, October 10, p. 693) raises a most important suggestion. While I have no experience of criminal cases, about which Dr. Tredgold was particularly making his point, I have been called on four separate occasions to give expert evidence in cases of alleged negligence, twice by the defence and twice by the plaintiff.

An expert is invited by one or other side to give an opinion, which in the first instance is written, then amplified in several private conferences, and later expounded publicly in the witness box. Try as one may to keep an open and fair mind, it is almost impossible to escape being influenced by the fact that one's advice has been obtained to help one side only. If one's answers in the examination-in-chief seem to favour the opposition, then one can be sure of a lengthy cross-examination, one of the most difficult experiences that can befall a responsible person. I speak with feeling, having on one occasion spent 14 hours in the witness box.

Questions are designed to show that counsel's case is right and the opposite view wrong. In many trials—for murder, fraud, theft, etc.—this demonstration works very well. The result must be either black or white, right or wrong, guilty or not guilty. But a medical opinion often does not fall into one of two such clear-cut categories. An opinion is not either quite black or quite white, but rather a mixture of grey and off-white. Likewise, it may not be possible to answer questions put in cross-examination by a direct yes or no. If pressed, a witness may be influenced towards giving the answer most favourable to his own side. Such an answer may not fairly describe the true clinical state or be an accurate physiological explanation.

Is this all too pedantic? I think not. The onus of proof lying with the plaintiff, it is not sufficient for the defendant to be shown to be *partly* to blame. He is rather 100% negligent, or not at all, which may be unfair to the injured patient. The case of *Woolley and Roe* v. *Ministry of Health* (*Journal*, April 17, 1954, p. 940) is the clearest and most tragic example of this type. There have been others since, the most recent being *Moore* v. *Lewisham Hospital Management Committee*, and I have no doubt new ones will occur from time to time.—I am, etc.,

University College Hospital, London, W.C.1. R. W. COPE.

Inoculation Clinics

SIR,—The introduction of a polyvalent virus vaccine for influenza now, and the possible introduction of a common cold vaccine in the future, may perhaps mark a welcome advance in preventive medicine. This could mean that there would be no less than seven diseases for which immunization is desirable in this country. In order to get as many people as possible protected from all these diseases (and, no doubt, more will be added to the list) some urgent rethinking is required.

If the general practitioner is to give these mass injections it would make serious inroads into his time for his other work. Moreover, many doctors have not the equipment and secretarial help for injections on a very large scale. We believe that wholesale inoculations cannot be easily undertaken in doctors' surgeries, and we think that the simple technique of subcutaneous injecting of large numbers *by doctors* is a waste of their valuable time.

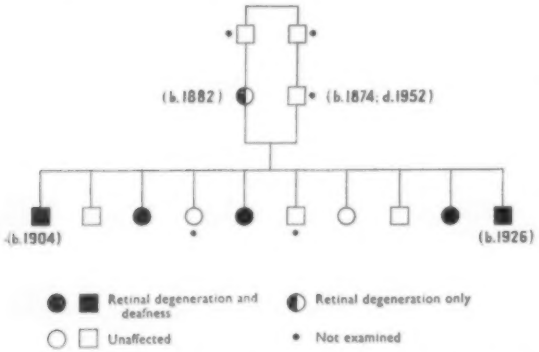
We think that inoculation clinics should be set up in all centres of population under the supervision of the public health authorities. These could be staffed by part-time helpers under supervision, perhaps recruited from Red Cross and St. John members, who could be quickly trained in simple injection technique. Sessions, which should be well publicized, should be arranged in the afternoon for mothers and children, and after working hours for the remainder. Each person should be provided with a card in an indestructible plastic case, on which details are recorded. A register would also be kept at each clinic for the benefit of the statisticians.—We are, etc.,

C. G. WINDSOR.
Walton-on-Thames. R. M. EMRYS-ROBERTS.

Retinal Degeneration and Nerve Deafness

SIR,—Your annotation entitled "A New Genetic Syndrome" (*Journal*, October 10, p. 688) brings to mind a family in South-west Scotland, seen in 1954–8 in my previous practice. The inherited defect here is retinal degeneration with nerve deafness. Polydactyly, obesity, and diabetes are not present. Mental retardation is debatable.

I examined 8 of the 10 surviving children of this first-cousin marriage. Five show both retinal degeneration and nerve deafness; three are normal; of the other two, one is probably not affected, and the other is doubtful. The mother is alive, and has retinal degeneration but not deafness. The father, who died in 1952, is said to have had normal sight. None of the many grandchildren examined shows retinal defect.



Above is a rough family tree. The distribution seems as expected, if the mother is a pure recessive for retinal degeneration and the father a carrier. But how the deafness links up had better be left to someone with some knowledge of genetics. The association of deafness with retinal degeneration is unlikely to be coincidental.—I am, etc.,

Wigtownshire. H. A. LANG.

Kartagener's Syndrome and Fibrocystic Disease

SIR,—Being interested in this syndrome, may I be allowed to make some comments on the excellent paper by Dr. N. M. Brown and Mr. A. N. Smith (*Journal*, October 17, p. 725)? The incidence of dextrocardia is difficult to estimate. Many published series are somewhat biased in the selection of their materials. Probably a better index is the figure obtained from large mass-miniature radiography units. Ramsay[1] has estimated that 1 in every 11,000 people has dextrocardia in this country. Calvert *et al.*[2] have collected several series and found an overall incidence of one dextrocardia in every 9,000 people. It is also difficult to estimate the incidence of bronchiectasis in cases with dextrocardia. It is well recognized that bronchiectasis can be present without any symptom; on the other hand, a mere productive cough is no proof of bronchiectasis.[3] There is no evidence that routine bronchography was carried out in each case in any large series of dextrocardia. However, combining data from several sources, Calvert *et al.* estimated that the classical triad of Kartagener's syndrome was present in 1 out of 60,000 population. Oeri[4] first recorded the association of the triad, but Kartagener was the pioneer in establishing the syndrome as a clinical entity. But it is not widely known that all the cases described by Kartagener and his colleagues were not typical examples of this syndrome.[2] Calvert *et al.* were able to collect 114 cases of the classical triad, including 4 cases of their own. The aetiology is not yet known, and various theories have been put forward—and further discussion on this line is beyond the scope of this short letter.

It is certainly interesting to read the first recorded case of this syndrome associated with fibrocystic disease. The association of mucoviscidosis and bronchiectasis is well known. Hence a similar defect has been postulated in the uncomplicated cases of bronchiectasis,[5] but it is rather unusual to find mucoviscidosis in the average patient suffering from this common malady. Many recorded cases of Kartagener's syndrome have been thoroughly investigated, and post-mortem reports are available in others[6–8]; but fibrocystic disease has never been found in this condition. Interestingly, however, congenital abnormality in the resected specimens of the lung was noted in two cases.[9 10] Imperfect pneumatization of the mastoid was described by Andrews,[11] and consanguinity of parents has been recorded in several cases.[2]

Lastly, it appears that the patient with the fibrocystic disease did not have a transposed lung, as bronchiectasis was noted in the lingula and the left lower lobe (although in a previous paragraph he was stated to have a left middle and lower lobe affection). Such cases of visceral inversion excepting the lung have been described.[12] Abnormal subclavian vessels have been found in Kartagener's syndrome.[13]—I am, etc.,

London, N.4. SAMIR K. GUPTA.

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Barbiturate Deaths

SIR,—Your annotation on increasing barbiturate deaths (*Journal*, October 17, p. 751) correctly points out that the problem lies in prevention. Two methods of preventing those deaths due to suicide were not mentioned in your annotation. (1) A long-term measure for which there is an overwhelming need is increased psychiatric training of medical students. (2) A practical method capable of immediate application is widespread use of oral combinations of bemegride ("megimide") with barbiturates whenever the latter are required in sedative or hypnotic dosage. In fact there is a negligible difference in cost, but even if the combined medication were more expensive the greatly reduced risk of death after accidentally or suicidally high dosage would outweigh the expense in saving of life. Regarding safety, I hope soon to publish results of a series of patients treated with continuous sleep therapy modified by using a bemegride/barbiturate mixture, in which doses of the order of 3 g. (45 gr.) of amylo-

barbitone with 10% bemegride in divided doses daily for 10 days were administered without evidence of overdose or any cause for alarm. In fact, the more of the mixture swallowed, the greater the relative effect of the bemegride, so that instead of going into coma the patient is more likely to have a convulsion.—I am, etc.,

Hailsham, Sussex. R. NEVILLE.

SIR,—In a recent annotation (*Journal*, October 17, p. 751) you reported on the increase in deaths from barbiturate poisoning and stated that something more than prescribing small quantities is needed. This of course is quite true, as potential suicides are very adept at hoarding their supplies. In view of this I feel I must report a recent case.

The patient was known to have suicidal tendencies, and on this account "phenaglate" capsules were prescribed. These contain quinalbarbitone sodium 50 mg., phenobarbitone 25 mg., and bemegride 7.5 mg. The patient took the 24 capsules very soon after he got them, and when I saw him about two hours later he showed no signs whatsoever of barbiturate poisoning. He told me later that he went for a walk later that evening and felt perfectly well.

I feel that this case may be of interest, as it proves how the harassed practitioner can be saved time and worry by this combination of bemegride with the barbiturates, not to mention the saving in hospitalization and even life itself.—I am, etc.,

Newport, Mon. D. T. HEFFERNAN.

Rhesus Tests

SIR,—Much technicians' time and Rhesus serum must be expended in determining the rhesus group of men married to Rhesus-negative women. Is this testing really necessary? It is already known statistically that most of these women have Rhesus-positive husbands, and, whether the man is found to be Rhesus-negative or not, a specimen of mother's blood is taken at the 34th week and cord blood from the baby at birth.

In my opinion the testing of a prospective father's blood is of no value to the obstetrician and merely serves to increase the apprehension of the patients concerned. To my mind a father's blood should be tested only after antibodies have been detected in the expectant mother's serum, and the vast majority of those men married to Rhesus-negative pregnant women should be left alone.—I am, etc.,

Gateshead, 11. T. L. C. DALE.

Thrombo-endarterectomy for Atherosclerotic Occlusion

SIR,—May I refer to the case I reported of atherosclerotic blockage in the left subclavian artery treated by thrombo-endarterectomy (*Journal*, October 17, p. 734)? Six months after a dramatic improvement following the thrombo-endarterectomy a mid-forearm amputation was done.

The patient was unwilling to leave her home town when pain in the hand returned four months after the operation, and Mr. J. C. Coates, to whom I am indebted for clinical details, had to look after her. Pain in the left ring and middle fingers necessitated amputation of the ring finger at the middle interphalangeal joint and of the middle finger at the proximal interphalangeal joint. Shortly after these amputations, which healed, the index and little fingers became blue and the radial pulse impalpable. Mr. Coates describes her a few days later "in a shocking psychological state with intractable pain in the whole hand extending above the wrist, the pain, however, being relieved by an upper dorsal ganglion block. The fingers started to go gangrenous and a mid-forearm amputation with evidence of good bleeding was done."

Dr. T. W. Sutherland reported on the specimen—"a clean amputation, radius 16 cm. long with no naked-eye signs of gangrene. Histology showed extensive organized thrombus occluding the ulnar artery; organized thrombus also present in the superficial palmar arch, a palmar digital artery, and in digital artery of the thumb and index finger. There is no evidence of any primary disease of the arteries in the sections examined." He considered the thrombus possibly the result of ischaemia, and had no doubt that organized widespread thrombosis of this sort must lead to gangrene.

I draw attention to the absence of any primary disease found in these arteries.—I am, etc.,

Leeds, 1. H. S. SHUCKSMITH.

Birth Weight and Maternal Smoking

SIR,—Dr. C. R. Lowe, in his paper on the above subject (*Journal*, October 10, p. 673), demonstrated that the babies of women who smoked were smaller than those of women who did not. He concluded that smoking during pregnancy substantially retarded foetal growth, and suggested that either tobacco exerted a direct pharmacological action on the foetus or else acted by restricting the placental circulation. Dr. E. C. Wood (*Journal*, October 31, p. 884) has pointed out that the evidence of Clement A. Smith regarding the effect of maternal nutrition conflicts with that of A. M. Thomson quoted by Dr. Lowe. Like Dr. Lowe, however, he seems to assume that it is the children of mothers who smoke who are the "abnormal" group.

Dr. Lowe's finding that surgical induction was required significantly more frequently in the case of non-smoking mothers suggests a further possibility: that it is the larger babies of non-smoking mothers which are abnormal. Many people who give up smoking compensate by eating sweets and chocolates to excess, and this may result in high blood-sugar levels for a considerable part of each day. Diabetics are known to produce abnormally large babies.[1] I suggest that this may be the results of the diabetics' high blood-sugar levels, and that this same mechanism may be operative in the case of women who consume sugar and sweets to excess. Since carbohydrates are the cheapest foods it is proteins which are commonly deficient in malnutrition. The lack of relationship between dietary deficiency and birth weight is therefore understandable.

It would be interesting to know if a relationship between excessive consumption of sweets and high birth weight exists. The fact that the highest proportion of babies weighing over 9 lb. (4 kg.) were born to mothers who gave up smoking in early pregnancy (Table I in Dr. Lowe's paper) favours this hypothesis, as does the finding that non-smoking mothers were heavier than those who smoked.—I am, etc.,

Public Health Department, Barton-on-Humber. J. S. ROBERTSON.

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SIR,—When Dr. C. R. Lowe writes (*Journal*, November 7, p. 957), "Had I reported that mothers fed on haggis to the music of the bagpipes had small babies, others as well as Dr. Hawkins might have been sceptical," how very right he is. But why is he very right? For the very good reason that he is very wrong.

If he turns to the *Guinness Book of Records* he will see that the largest inhabitants of the British Isles, with an average height of 5 ft. 9½ in. (177 cm.), are to be found in the County of Sutherland. Knowing, as I'm sure he must, that the larger the baby at birth the larger the adult, he will be bound to admit that Sutherland babies are larger than average. But haggis eating and the playing of the *piob mhor*, or great Highland bagpipe, is almost endemic in Sutherland. Hence it must be obvious that haggis eating, the playing of the pipes, and large babies are intimately connected. I even go so far as to suggest, in the language of the statisticians, that the correlation is significant.—I am, etc.,

St. Austell, Cornwall. DOUGLAS G. WILSON CLYNE.

Steely Eyes and Pain

SIR,—Dr. W. A. Bourne's letter (*Journal*, October 24, p. 827) referring to your annotation on this subject confirms the impression that brown eyes are associated with a low threshold to pain and suggests that retinal pigmentation and dark hair occur with brown eyes in persons with a Mediterranean strain. At the London Hospital the lowered threshold to pain was well recognized in members of the Jewish race, in whom these physical features are present, and I have often observed it since. Unfortunately I cannot recall the colour of the eyes in red-haired Jews; perhaps one of your readers can help.

Increased excitability or over-reaction to pain may be, as Dr. Bourne says, a different thing from a lowered threshold; indeed, dark-eyed, grey-, and even blue-eyed individuals may alike react to pain even before it is inflicted.—I am, etc.,

Hove, Sussex. G. M. WAUCHOPE.

"Niamid" in Mongolism

SIR,—During a clinical evaluation of a mono-amine-oxidase inhibitor N'isonicotinoyl-N'-(β-N-benzyl carboxamido-ethyl) hydrazine ("niamid") an unexpected finding was a good response in mongolism. Such patients are usually pleasant, affectionate, and easy to care for, but some become apathetic, listless, morose, and quite lacking in initiative, and it was in this type of case that the improvement was observed.

Niamid was administered orally in doses rising from 30 to 75 mg. daily to a group of 27 mongols, whose ages varied from 6 to 35 years, at this hospital for mental defectives. One mongol has received the drug for eight months, the others for three months. Controls were not used, but 14 of these patients had had a variety of other tablets preceding this trial without any effect on their mental state being noted, so it is considered that the beneficial effects observed were due mainly to the drug and not to the "tablets" or to increased attention.

Males			Females			Total
Improved Markedly	Improved	No Response	Improved Markedly	Improved	No Response	
—	4	7	3	14	1	29

The seven male patients who showed no response were alert and active before treatment. Among the females, three improved markedly; one, a 35-year-old imbecile who had never spoken, gradually began to speak in monosyllables, and now, after two months, converses in short sentences; her physical activity has also increased, and she undertakes simple domestic tasks. Two other females also improved markedly, 14 others improved moderately. In all who improved there was manifest increase in mental and physical activity, and they became more cheerful and vivacious. These changes were noticed by the parents, nursing staff, schoolteachers, and occupational therapists. No serious side-effects have been noted, but one mongol became very overactive, almost hyperkinetic, but this subsided when niamid was withdrawn. This effect has been observed in other clinical types, but can be controlled by the addition of a suitable phenothiazine.

Himwich and Fazekas[1] reported a decrease in cerebral oxygen utilization and sugar uptake in both mongolism and phenylpyruvic amentia, and suggested that the cerebral metabolism is decreased in both conditions and that this might be due to an enzyme deficiency. The amine-oxidase inhibitors are believed to increase indirectly the amount of cerebral serotonin and noradrenaline, and this mechanism may account for the increase in physical and mental activity of these apathetic mongols. Phenylpyruvic amentia should also improve on such therapy if the suggestion of Himwich and Fazekas is correct.—I am, etc.,

Hensol Castle Institution, Pontyclun, Glamorgan. T. S. DAVIES.

REFERENCE

[1] Himwich, H. E., and Fazekas, J. F., *Arch. Neurol. Psychiat. (Chicago)*, 1940, **44**, 1213.

Treatment of Migraine

SIR,—Dr. Christopher Heath's letter on migraine (*Journal*, October 17, p. 759) interests me, and I agree with his remarks about this tiresome minor complaint. He writes, "Its manifestations are aggravated by relaxation." I would go further and suggest that attacks are encouraged by relaxation and are inhibited by activity and concentration.

This opinion is based on long personal experience, as I have been annoyed by attacks of idiopathic migraine (with severe visual disturbance lasting an hour or two) for 50 years. Underestimating the average frequency at twice a quarter, this gives a total of at least 400 attacks. But has migraine hampered me in work or pleasure? Scarcely at all, for most attacks have come on at times of inactivity, torpor, or mental vacuity, typically while shaving or sipping one's early-morning tea. Never once in student days did migraine come on while I was taking an examination. Nor can I recall getting it during trench warfare in 1916–17. In 34 years of practice I never once had it while giving an anaesthetic, delivering a baby, suturing, or during the always anxious third stage. Never has it interfered with a day's shooting, or a visit to the theatre.

I apologize, Sir, for all these personal details, which prove nothing. But I am left with the strong impression that migraine does not occur during periods of stress and activity.—I am, etc.,

Freshford, Somerset. EDWARD CHAPMAN.

Organic Aetiology in Psychiatry

SIR,—It is sad that Dr. William H. Shepley is retiring when it is clear from his letter (*Journal*, November 7, p. 958) that his attitude is so much more advanced than that of many a psychiatrist remaining in practice. He could not have chosen a better way, however, of marking his retirement than by admonishing against the still-too-prevalent teaching of some psychiatrists in this country that in every case of mental illness there must be an organic cause. Unfortunately many of those

other specialists who are responsible for the training of the next generation of doctors also tend to retain that out-moded mechanistic approach for *all* illness. The patients who are used for teaching purposes are usually those in whom advanced pathological changes can be demonstrated, while those who have been fully investigated and shown to have "nothing wrong" are returned to the family doctor. It is not surprising that when the newly qualified doctor first sees his patients in general practice he is likely to be at a loss to know what to do for them.

Medical students from two teaching hospitals sit in with me during evening surgeries, and I am for ever impressed by their astonishment at the way patients present themselves with symptom-complexes seldom seen at hospital. I am not always impressed, however, with the instruction received by these students at hospital. Not long ago one lecturer was quoted as saying: "You must not take any notice of all this psychological nonsense—you must remember we doctors are scientists."

I should like to join with Dr. Shepley in his submission that the medical curriculum needs to be radically amended by the addition of specific instruction in psychosomatic correlations for students attaining access to the wards and thereafter throughout. I am certain that this will be welcomed by all who have been able to recognize the high incidence of illness where such instruction would be readily applicable in everyday hospital as well as general practice.

It is appreciated that not all medical students become general practitioners, but even those who choose to specialize might well benefit from some experience of general practice—and this can best be taught by those who practise it. I would therefore like to add to Dr. Shepley's submission, in order to implement it as well as to do more than pay the usual lip-service to the part played by the family doctor (the backbone of the profession, the front-line of the National Health Service, etc.), that every medical school should have on its staff general practitioners to help in this important aspect of the training of future doctors.—I am, etc.,

London, N.W.3. PHILIP HOPKINS.

The Wolfenden Report

SIR,—I hope nobody will be misled by Mr. Kenneth Walker's unbalanced letter (*Journal*, October 31, p. 883). He might have waited to get the facts. One newspaper stated that this was not the first time that this poor lad had been charged with this offence, and it is conceivable that the authority who refused bail, the magistrates or judge in chambers, may have thought that he was a menace to small boys, that he was not under effective control at home, and that it was their duty to keep him in custody. I simply do not know, nor at the time of his writing did Mr. Walker. It is also conceivable that the Wolfenden Report itself was the genesis of this tragedy: "That Sir John Wolfenden—you know, the chap on the T.V., he says these things don't matter a bit. He says they're not crimes," that is the sort of summary of the report that has percolated down to the age-group and social state to which this poor youth belonged.

In his short letter Mr. Walker made two grossly misleading statements: (1) "While the Church has come down courageously and strongly on the side of implementation of the Wolfenden report, the medical profession . . ." This is untrue, the Church has done nothing of the sort. The facts are: In the House of Lords debate on the report (*Hansard*, December 4, 1957), the Archbishop of Canterbury and the Bishop of St. Albans spoke in favour of the homosexual recommendations, the former making the reservation that sodomy should remain a crime even with consenting adults, while the Bishops of Rochester and Carlisle spoke uncompromisingly and sternly against them. In the Church Assembly (*Church Times*, November 27, 1957) 155 voted in favour of the recommendations, 138 against, and 407 abstained from voting. The General Assembly of the Church of Scotland "by a great majority endorsed their committee's opposition to the Wolfenden findings on homosexuality" (*The Times*, May 27, 1958). So much for "courageously and strongly." That is the measure of Mr. Walker's accuracy and sense of responsibility.

(2) "No political party regards the matter as an urgent or even as an important one." Anybody who listened to the debate in the House of Commons or read the account of it in *Hansard* (October 26, 1958) would know that this is not a party matter at all, there were pro-Wolfendens and anti-Wolfendens in both parties, and none of the speakers thought the matter was unimportant; on the contrary they almost all showed that they realized that fundamental issues were at stake which could affect any home in the country, generations unborn, and individual liberty. The threat to youth was repeatedly stressed by many, among whom were the two doctors, belonging to different parties, who both spoke against the recommendations.

Mr. Walker's last sentence—"Do we wait quietly until another boy has hanged himself?"—has a touch of hysteria, shirking grim realities, putting the blame on somebody else, and seeking an easy solution which would, in my view, cause a large number of tragedies in the years ahead of the same unsavoury sort.—I am, etc.,

Beckley, Rye. C. G. LEAROYD.

Thalidomide

SIR, — Having used "distaval" (thalidomide) extensively as a nightly sedative for all types of geriatric patient, including many with senile atherosclerotic conditions, for well over a year, I was surprised to read of Dr. A. K. K. Nyazai's experience (*Journal*, October 31, p. 888) that "prolonged diurnal drowsiness" was produced in an unmentioned proportion of cases. This has certainly not been our finding: in fact, the absence of after-effects is one of the drug's advantages, the others being rapidity of action, low toxicity, and compatibility with alcohol. Only rarely have we found it necessary to reduce the usual adult dose of 100 mg. because of slight drowsiness the following morning. The addition of amphetamine, as Dr. Nyazai suggests, would, I feel, interfere with the drug's sedative action without producing any worth-while advantage.—I am, etc.,

Geriatric Unit,
Southampton General Hospital. T. N. RUDD.

Ferrous Fumarate

SIR,—Drs. H. T. Swan and G. H. Jowett draw attention to the place of ferrous fumarate in the treatment of iron deficiency (*Journal*, October 24, p. 782), while a contemporaneous annotation (p. 812) takes a broader view of such deficiency and stresses the importance, in certain cases, of a search for occult blood loss from the gastro-intestinal tract.

The problem of the effect of oral iron on tests for occult blood loss in the stools is a vexed one, and a review of the last 50 years of medical writings on this

subject reveals an extraordinary and inexplicable divergence of opinion. However, in the last decade it has been generally accepted that oral iron does not give false positive results with such tests, and that therefore the investigation and treatment of sufferers from iron deficiency may proceed together. Using the benzidine test and the orthotoluidine test—the latter the tablet test of the Ames Company (London) Ltd.—I have by *in vitro* and *in vivo* tests confirmed that this is correct procedure with all oral iron medicines except ferrous fumarate. The Ames Company manufactures two types of orthotoluidine tablet known as "hematest" and "occultest," the latter being a more sensitive indicator for blood, but even the less sensitive product gives a positive result with the faeces of a normal patient on a meat-free diet who is receiving ferrous fumarate by mouth.

The clinician who favours the orthotoluidine tablet tests should therefore ensure that an investigation of the gastro-intestinal tract for occult blood loss does not coincide with the oral administration of ferrous fumarate.—I am, etc.,

Edinburgh, 10. DAVID G. ILLINGWORTH.

Tongue-tie

SIR,—Mr. H. St. John Rumsey (*Journal*, October 17, p. 761) says that in every case referred to him the tongue had ample freedom for all its positions required for fluent speech. My experience is the same. I have not seen a case of congenital tongue-tie where the movements of the tongue have been impeded in infancy or where the speech has been affected in later life. Scores of cases have been referred to me, but I never treat them surgically.

In all normal infants the frenum of the tongue is much more prominent than in adults, and it is my belief that congenital tongue-tie is largely a figment of the imagination of mothers, midwives, and doctors. Acquired tongue-tie, due to trauma (including snipping of the frenum), inflammation, and tumours, is in a different category.

Mr. Denis Browne (*Journal*, November 7, p. 952) says that tongue-tie is a rare but definite and important congenital deformity. I would like to emphasize the word "rare" and utter a prayer that his letter will not lead to a further wave of frenum snipping, and would suggest that these rare cases should be treated only in plastic units or children's hospitals.

Careful inspection of Fig. 1 (Mr. Denis Browne) gives one the impression that there is a small globular tumour in the region of the frenum and that the picture has been retouched.—I am, etc.,

Rotherham, Yorks. ERIC COLDREY.

Carcinoma of Oesophagus in Association with Tylosis

SIR,—In a previous letter we reported an association between keratosis palmaris et plantaris (tylosis) and carcinoma of the oesophagus in two Liverpool families (*Brit. med. J.*, 1957, **1**, 945), and we later dealt with the problem in more detail (*Quart. J. Med.*, 1958, **27**, 413). This letter is to report an additional cancer case in one of the tylotic members known to be at risk (IV.2 "S" pedigree).

M.G., aged 49, was admitted to hospital in August, 1959, complaining of difficulty in swallowing for the previous five months. Oesophagoscopy showed a large neoplasm 25 cm. from the incisors, and the thoracotomy subsequently revealed a carcinoma of the middle third of the oesophagus. Gross adenopathy was present and the tumour was surgically inoperable, but some symptomatic relief was obtained by the insertion of a Monseux-Bourbour tube. The biopsy was reported on as showing a well-differentiated squamous carcinoma.

The case emphasizes the difficulty in knowing how best to deal with our tylotic patients, who are clearly very liable to develop the oesophageal lesion. In this instance, although the patient knew that his sister and two of his brothers had all died of the neoplasm, he had not sought medical advice for several months after symptoms had begun. Clearly individuals need handling in different ways, and the matter would seem to be best dealt with by the family doctor who, having been given details of the pedigree, knows those who are at risk.

In the two and a half years since our original letter carcinoma of the oesophagus has developed in a further three members of the families, and the total number of those known definitely to have had the neoplasm is now 19. The mean age of the carcinoma cases is 45.1 years with a standard deviation of ± 9.51 years. Statistical analysis shows that 95% of tylotic individuals in our families can be expected to develop the neoplasm between the ages of 26 and 63, provided they do not die from some other cause. Furthermore, from a knowledge of the number of tylotics over 26 years of age we estimate that on average we can expect one new case of the oesophageal carcinoma every two years.—We are, etc.,

C. A. CLARKE. R. B. MCCONNELL.
W. HOWEL EVANS. P. M. SHEPPARD.

Liverpool.

A New Penicillin

SIR,—On October 24 last notification was sent to medical practitioners that "broxil," the first of the new penicillins derived from the isolation of 6-aminopenicillanic acid was available to them in limited quantities for further clinical evaluation. This product and its properties were accurately described as follows:

"'Broxil' is the potassium salt of 6-(α-phenoxypropionamido)-penicillanic acid. Its spectrum of bacteriological activity resembles that of penicillin G and penicillin V. Given orally, however, it gives blood levels two to three times as high as those following penicillin V and at least equal to those following intramuscular injections of penicillin G."

In your issue of November 7, p. 940, there appeared an annotation entitled "A New Penicillin" which was largely devoted not to an examination of "broxil's" declared properties but to a lengthy recital of the properties that it does not claim—including activity against Gram-negative bacteria and resistant staphylococci. The manner in which this information was presented, and the whole tone of the annotation, seemed designed by your contributor to denigrate the important attributes possessed by "broxil." This impression was enhanced by the irrelevant introduction of references made at a recent B.M.A. conference to work now proceeding at Brockham on the development of penicillins with properties widely differing from those of "broxil." Reporting of this kind does less than justice to the standards of objectivity one is entitled to expect of a professional journal, and is calculated to cause confusion where none existed before.

There is no doubt that your report has already excited eager interest in quarters where criticism of a British product is welcomed with open arms. It is presumably no part of the function of a professional journal to concern itself with commercial problems, but it is unlikely that you are wholly unacquainted with the formidable opposition that confronts a firm engaged in advancing British interests in those fields of pharmaceutical manufacture which have hitherto been the virtually undisputed domain of American enterprise. The early history of penicillin reminds us that brilliant research work is not sufficient in itself to secure for the country of its origin the benefits that flow from development and large-scale manufacture. Nor does the present state of international patent law safeguard an originator against attempts by imitators to claim the credit and reward for his discovery. It is for this reason that a manufacturer delays at his peril the public announcement of significant advances in his research and development programme. These are the harsh circumstances of commercial life which must constantly engage the vigilance of any manufacturer who hopes to see his research endeavour justified in terms of new and better products for medical use that can more than hold their own, in terms of quality and price, in a ruthlessly competitive world market.

This situation can, very properly, have no bearing on the manner in which a professional journal conducts its affairs. But it explains why a manufacturer takes the strongest exception to an oblique attack, giving comfort to foreign competitors, which is based not on an objective appraisal of a product's declared properties but upon its failure to possess attributes that are not claimed for it.—I am, etc.,

C. D. W. STAFFORD,
Managing Director.

Beecham Research Laboratories Ltd.,
Brentford, Middlesex.

Anti-tuberculosis Vaccines

SIR,—I have read the second report of the Tuberculosis Vaccines Clinical Trials Committee of the Medical Research Council (*Journal*, September 12, p. 379) with great interest. The Committee has done a great service in confirming beyond doubt the protective value of anti-tuberculosis vaccines, especially B.C.G. The findings are of very far-reaching importance and should help the cause of B.C.G. vaccination in most countries of the world.

My thoughts after I had read the report ran in different directions. Firstly, towards the U.S.A. and the seventeen prosecutors in "The Case against B.C.G." (*Journal*, June 6, p. 1423), to whom the fresh evidence contained in the M.R.C. report must have come as a surprise. Secondly, to the memory of the late Dr. A. Q. Wells, of Oxford, who is unfortunately not alive to-day to see the results of the use of the vaccine that he so meticulously developed in his laboratory. Thirdly, towards the Scandinavian countries whose claims on the protective value of B.C.G. vaccine have largely been substantiated by the M.R.C. trials. To Dr. Knud Tolderlund, of the State Serum Institute, Copenhagen, it must be a great source of satisfaction—and relief—that the vaccine prepared under his supervision and used in the M.R.C. trials has given such uniformly satisfactory results despite the unavoidable fluctuations in the viable counts of the vaccine from batch to batch. Fourthly, to the grand old gentleman, now nearing 90, living in the Pasteur Institute, Paris, Dr. Camille Guérin, whose heart the M.R.C. report must have gladdened beyond measure. Lastly, to the Unicef, which is spending millions of dollars on the mass B.C.G. vaccination programmes in various countries in the world. The report should be a source of great strength to the various national governments and their tuberculosis advisers in the furtherance of the B.C.G. vaccination campaigns. The report should also serve to smother any lingering doubts about the safety and value of the vaccines.

From the practical point of view, the question is, "Can similar results be obtained after B.C.G. vaccination in different countries?" Obviously the results in different countries will vary with the prevailing epidemiological conditions, but that does not detract from the value of the vaccines as a preventive measure. It must, however, be emphasized that the highest standards must be maintained in the production of the vaccines, which must be really potent and must be applied in the field with the greatest care. The M.R.C. report has further served to underline the uniform success of the intracutaneous method of administration of B.C.G. vaccine recommended by the W.H.O. Expert Committee, and exclusively followed in the mass B.C.G. vaccination campaigns throughout the world.—I am, etc.,

K. S. RANGANATHAN.

Madras.

Service Psychiatrists

SIR,—Dr. J. T. Wilde (*Journal*, November 7, p. 953) describes how the members of a medical board crouched under a table while the patient under examination remained standing at attention. The man was considered to be "incapable of preserving himself from common dangers" and was labelled psychotic.

I was once attending a debate in the House of Lords, then held in Church House, Great Smith Street, when the "imminent warning" was sounded. Not a soul moved. Sir John Simon, then Lord Chancellor, in full-bottomed wig and gold-embroidered gown, was speaking from in front of the woolsack, when a V1 was heard approaching. It cut out overhead. For perhaps a second he paused to listen, and then continued his remarks, in a tense silence. The bomb exploded on a building in Victoria Street about 100 yards (92 m.) away. No one moved, and the debate continued unruffled by this unseemly interruption. Not one of the noble lords present, I understand, has since been certified.—I am, etc.,

W. A. LETHEM.

London, W.5.

Press Publicity

SIR,—With reference to Dr. Donald V. Bateman's letter (*Journal*, November 7, p. 954), how can medical men be protected from undesirable attentions from the press? I have been for over ten years chairman of the Medical Advisory Board of the National Marriage Guidance Council, and sometimes take part in the selection and training of its counsellors. At the request some years ago of the Church of England (of which I am not a member) I agreed, naturally without fee, to write something about the middle-aged man for guidance to clergymen who have to counsel them. Eventually, after much labour and thought, I produced a 16-page pamphlet. On its publication I was inundated with calls from the press. My receptionist has always refused to give the telephone number of the hospital where I work. To my surprise, on finishing a session I was trapped by a reporter who had travelled nearly 20 miles in a taxi and waited over an hour to see me. What guidance can be given to the hapless doctor? Since many leading

medical journals are to be found in every public reading-room, should the medical man write only for publications with a closed circulation ?—I am, etc.,

London, W.1. ALFRED TORRIE.

SIR,—It is a pity that Dr. D. V. Bateman (*Journal*, November 14, p. 1024) should react to a first-class occasion with pin-pricking criticism. Doctors with whom I spoke all agreed with Dr. Talbot Rogers that Norwich was a memorable clinical meeting. One elegant item, again in the view of doctors who were present, was the caesarean section by which the Lord Mayor delivered one of his citizens of a baby. Not every day does this happen and on closed-circuit television, too, before 500 doctors, students, and nurses. There was therefore legitimate public interest in this part of the programme.

Dr. Wand and his colleagues spontaneously and generously decided to mark the occasion with a small B.M.A. gift. It was Dr. Wand's short but dignified speech that gave some information. In addition, there were others, less aloof in spirit than Dr. Bateman, who saw that this was good medical news. And so we of the lay Press, who fully understand and readily accept exclusion from clinical demonstrations, obtained the facts, although, as Dr. Clegg points out, there was no B.M.A. handout.

Permission to use the patient's name was given. At no time was the patient worried. To save her trouble, the presentation was made to her husband, understandably as delighted by the day's events as she was. Indeed, no one at Norwich happily seemed to have Dr. Bateman's quaint outlook.—I am, etc.,

The *Daily Telegraph and Morning Post*, London, E.C.4. JOHN PRINCE.

Cost of Treating Baldness

SIR,—A few days ago a patient came to ask me if she would benefit from a course of treatment at a trichologist's clinic. She thought she was going bald. She had been told that she needed treatment, and that a complete cure was guaranteed in six months. The cost—119 guineas, or 99 guineas if paid in advance.

In fact she was not going bald, but it was necessary to refer her to a consultant dermatologist in order to convince her. He prescribed a simple scalp lotion. The cost to the patient one shilling. The cost to the State two shillings.

If one assumes the trichologist to be competent, his treatment ought to have been along the same lines as the dermatologist. This makes one wonder why the bill was to be £124 17s. more.—I am, etc.,

Marston Green, Warwicks. J. W. WARBURTON.

Christmas Gifts Fund Appeal

SIR,—I should like to remind your readers who have not yet responded to the President's Appeal (*Journal*, October 17, p. 755) that it is our custom to distribute the gifts some days before Christmas. I hope all who can will send their contributions marked "Christmas Gifts" to the Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19, as soon as possible. —I am, etc.,

London, S.W.19. F. A. JULER, Honorary Treasurer, Royal Medical Benevolent Fund.

Obituary

ALEXANDER MILLER, M.B., Ch.B., F.R.C.S.Ed. F.R.F.P.S.

Mr. Alexander Miller, visiting orthopaedic surgeon to the Victoria Infirmary, Glasgow, and honorary regional consultant in orthopaedics for south-west Scotland, died at his home at Jackton, Lanarkshire, on November 4. He was 55 years of age.

Alexander Miller was educated at Allan Glen's School and Glasgow University. He graduated M.B., Ch.B. in 1928 after a distinguished career in academic work, sport, and the corporate life of the university. He was then appointed to the resident staff of the Victoria Infirmary, Glasgow, and while working with Mr. James Russell developed the strong interest in orthopaedic surgery which was maintained throughout his career. He spent several years in orthopaedic centres in England, and studied the work of Sir Robert Jones, Mr. Naughton Dunn, and other outstanding authorities. He obtained his higher qualifications, F.R.C.S.Ed. and F.R.F.P.S., in 1931, and two years later returned to Mr. Russell's unit at the Victoria Infirmary. He was the first surgeon in the West of Scotland to confine his work to orthopaedic surgery, and his value was soon recognized. In 1939 a new orthopaedic unit was built at the Victoria Infirmary, with the aid of a grant from Lord Weir, and the Nuffield Foundation gave a substantial sum to develop the Philipshill annexe as a sectoral hospital for orthopaedic cases. The rehabilitation centre for miners at Uddingston has proved to be of great value. These developments were almost entirely the result of Miller's influence. He became widely recognized as an authority in this country and abroad. Last year he presided over the first meeting of the Scottish Orthopaedic Club, and he was also a former president of the Southern Medical Society of Glasgow. He played a full part in medical affairs in general. He was a member of the first Western Regional Hospital Board, and for eight years was an effective force in planning the policy of the National Health Service. In 1953 he was appointed a member of the Industrial Injuries Advisory Council under the Ministry of Pensions and National Insurance. A member of the British Medical Association for 30 years, he served as a vice-president of the Section of Orthopaedics and Fractures when the Association held its Annual Meeting at Aberdeen in 1939, and for some years he was a member of the Rehabilitation Committee and the Orthopaedic Group Committee of the B.M.A.

Miller was a man of many interests. He distinguished himself in various branches of sport, and as a young man played in the inter-city rugby football match. Recently he turned his attention to curling, and was president of the Scottish ice-rink club. He was also vice-president of the Glasgow Art Club and a council member of the Royal Philosophical Society of Glasgow. A man of great charm, he made friends readily, and to all he was known as "Sandy" Miller. His informed mind, his shrewd judgment, his ready wit, and his gift for conversation were obvious to a casual acquaintance. His greatest quality was evident only when the occasion required it. He was a man of great courage. He had courage of both kinds—the spirit which responds instantly to a challenge, and the fortitude which endures cheerfully when all hope is gone. His wife shared many of his interests, and great sympathy is felt for her at this time.—T. L. C.

J. McI. H. SMELLIE, M.B., Ch.B.

Dr. J. McI. H. Smellie, who was in general practice in Liverpool for many years, died at his home at Sefton Park on October 31 after a short illness. He was 64 years of age.

John McIldowie Hope Smellie was born at Libberton, Lanarkshire, on December 27, 1894, the eldest son of a

schoolmaster, and was educated at Lanark Grammar School. He studied medicine at Edinburgh University, where he graduated M.B., Ch.B. in 1917, having spent his final year, on the recommendation of Professor Halliday Croom, as resident physician at Livingstone Memorial Dispensary, Cowgate. He served in the R.A.M.C. with the Mesopotamia Expeditionary Force from 1917 to 1920. On his return he entered general practice in Sefton Park, Liverpool, and soon made his mark as a physician, especially in the fields of haematology and obstetrics. During the second world war he undertook many additional duties. He lost his home in the air raids of May, 1941. After a serious illness in 1948 he took his son into partnership and so was enabled to renew his great interest in literature, architecture, photography, and flowers. He was an active member of the Liverpool Medical Institution, on the library committee of which he served for many years; and this year he was a vice-president of the institution. He was also a member of the North of England Obstetrical and Gynaecological Society and was chairman of the Liverpool Division of the British Medical Association in 1955–6. He served also on the Liverpool Executive Council and local medical committee. In 1920 he married Miss Mary Clarkson, M.A., who survives him with his son and two daughters, all three of whom are members of the medical profession.

We are indebted to Lord COHEN OF BIRKENHEAD for the following appreciation:

Nearly 35 years have passed since Dr. J. McI. H. Smellie first asked me to see a patient. I recall the consultation clearly for two reasons. First, he had established the diagnosis of pernicious anaemia by blood counts and beautifully stained blood-films which he demonstrated to me; and, secondly, I had just read the paper by Minot and Murphy in the latest number of the *Journal of the American Medical Association* and thus had my first chance to advise a curative therapy. Three months later, he presented me with a record of blood counts and stained films which he had himself taken at weekly intervals—typical of all I learned later of his competence, skill, keenness, and thoroughness. He was a big man, of fresh complexion, with a boyish smile and alert, eager eyes. His voice betrayed his Scottish origin and upbringing, and though he admired increasingly the Liverpool Medical School, where his three children had been either medical students or house-physicians of mine, he loved to the end his own Alma Mater and never tired of singing the praises of the medical giants of the Edinburgh of his day. He was the best type of general practitioner—the friend, guide, and guardian of his patients. In their interests he worked unceasingly. Dr. Johnson's lines on Dr. Robert Levit are apt of him:

> "His useful care was ever nigh . . .
> His virtues walk'd their narrow round,
> Nor made a pause."

He was a shrewd diagnostician and kept himself abreast of any advancing knowledge which might improve the quality of care with which he could tend his patients. He was always present at a consultation—not only in the patient's home but in the consultant's room—and he believed there were few better opportunities for postgraduate education for both the general practitioner and consultant. He attended regularly lectures at the University and meetings of the Liverpool Medical Institution, which he served in many capacities, more recently as vice-president, and his colleagues testified to his experience and wisdom by electing him to many committees in the National Health Service. He will surely be inscribed in the book of gold as one who loved and served his fellow men.

Dr. R. BRADSHAW writes: With the passing of Dr. J. McI. H. Smellie we have lost one of the most prominent family doctors on Merseyside. He was deeply respected for his character, wisdom, skill, and knowledge by all his professional colleagues, and served his profession on many important committees. Nor were his interests confined to medicine: he was an expert motor engineer, and some of his work in the sphere of amateur photography can only be described as superb. He was deeply loved by his patients, and the large attendance at the funeral service on a bleak November morning notably attested the truth of the opening sentences of the memorial address: "Dr. Smellie was held in high esteem by the people of Liverpool, and was renowned among his profession; he was an example to us all." He was a true Christian both in thought and in deed, and he will be greatly missed, especially by those of us for whose families he had cared during his long years of practice in Liverpool. To his widow, his son, and two daughters a very deep and special sympathy is extended in their grievous loss.

H. B. DAY, *M.C.*, M.D., F.R.C.P.

Professor H. B. Day, emeritus professor of clinical medicine in the University of Cairo, died at Alton, Hampshire, on November 1. He was 79 years of age.

Harold Benjamin Day was born in London in February, 1880, the eldest son of the Rev. B. W. Day. Educated at Westminster School and at King's College, London, he went on to King's College Hospital with the Warneford entrance scholarship in 1897. Subsequently he gained the Sambrooke exhibition, the Rabbeth scholarship, and the junior, the second year, and the senior scholarships, qualifying M.R.C.S., L.R.C.P. in 1902. After qualification he held the appointments of house-physician at King's and house-surgeon at the Royal Free Hospital. He took the London degrees of M.B., B.S. in 1904, gaining the gold medal, and in 1905 he returned to King's as Sambrooke medical registrar. In the latter year he proceeded to the M.D., at the examination for which he qualified for the gold medal. In 1906 he was appointed registrar and tutor in the Government School of Medicine in Cairo, and four years later became professor of clinical medicine and physician to the Royal School of Medicine (Kasr-el-Aini Hospital), Cairo, and physician to the Anglo-American Hospital. Leaving Egypt on the outbreak of the first world war in 1914 to enter the R.A.M.C., he served throughout the war, mainly in France, and attained the rank of major. He was awarded the Military Cross in 1917, when the official citation read as follows: "He worked night and day for four days with magnificent fearlessness, tending the wounded, not only of his own battalion, but also of all others in the vicinity. At one moment he led a party of stretcher-bearers across the open and brought back fourteen wounded in daylight, in full view of the enemy. This, however, is only one instance of the many heroic acts which this gallant officer performed under heavy shell and machine-gun fire."

Day was admitted a Fellow of the Royal College of Physicians of London in 1918. He was demobilized from the Army in the following year, and then returned to Cairo. In 1922 the King of Egypt conferred upon him the Order of the Nile (Third Class) in recognition of the valuable services he had rendered. In 1925 Day took up the appointments of lecturer in forensic medicine and toxicology in the King's College Hospital Medical School and physician to the Royal Chest Hospital, and four years later he was appointed lecturer in and physician for tropical diseases at King's. In 1933 he again went back to Cairo, this time as professor of clinical medicine and director of the medical unit in Cairo University. When he retired from the chair in 1936 the title of emeritus professor was conferred upon him. Since then he had lived in the London area. He was twice married. First, in 1909, to Miss Ruth Witty, who died in 1914, and by whom he had one daughter, and secondly, in 1920, to Miss Winifred B. W. Hughes, by whom he had one son, now Dr. H. J. B. Day, surgical registrar at the Henry Gauvain Hospital, Alton.

H. McE. MORRIS, M.D., D.M.R.D.

Dr. H. McE. Morris, consultant radiologist to the Salford group of hospitals, died at Salford Royal Hospital on October 2. He was 60 years of age.

Hugh McEvoy Morris was born at Glenarm, County Antrim, on November 26, 1898, and was educated at the Christian Brothers School, Omagh, where he was a brilliant scholar, gaining first place in all Ireland in the senior grade. In 1915 he proceeded to the Queen's University of Belfast with a county scholarship, and graduated M.B., B.Ch. in 1921. He proceeded to the M.D. in 1926, and in the same year obtained the Liverpool D.M.R.D. After graduation he held the appointment of senior house-surgeon at the Mater Infirmorum Hospital, Belfast, and then was in general practice at Carcroft, near Doncaster, for a year or two. In 1926 he settled in Salford, becoming first of all radiologist to the Manchester municipal hospital services. Subsequently he became honorary radiologist to the Salford Royal Hospital, the Royal Manchester Children's Hospital, the Manchester Victoria Memorial Jewish Hospital, and the Eccles and Patricroft Hospital, and consulting radiologist to the Devonshire Royal Hospital, Buxton. Since the inception of the National Health Service in 1948 he had been in charge of the radiological departments at Salford Royal Hospital, the Hope Hospital, Salford, and the Royal Manchester Children's Hospital. During the second world war he served in Iraq and Ceylon as a major in the R.A.M.C.

E. B. writes: Outside his hospital work, Hugh Morris was a man of many interests. In 1934 he wrote *Medical Electricity for Massage Students*, which remains a standard textbook on the subject. He was chairman of the local board and president of the branch of the Chartered Society of Physiotherapists. He gave much time, help, and encouragement to the Cripples Help Society, and was recently honoured by being made a life member of the committee. He followed the fortunes of the Manchester United association football club with great interest, and gave them much professional help. He was in fact regarded by them as "one of the team." He was, too, a regular lunch-time visitor to the Manchester press club, and delighted in the lively interchange of witty talk and in the companionable atmosphere. Hugh Morris was "a character." Full of fun, lively of mind, unassuming, natural, and sincere, he was never afraid to be himself in any group. His marriage to Helen Cateaux brought him great happiness and a quiet restfulness of spirit. To visit the Morris's meant that one was at once welcomed into the warmth and living friendship of a real home. Throughout his illness Hugh Morris never gave up, but continued the work he so much enjoyed beyond the limits of his strength. "Hughie" will long be remembered with deep affection. The Salford scene has lost colour by his untimely death. Our deepest sympathy is extended to his mother, widow, brothers, and sisters, and to the three sons of whom he was so justifiably proud.

V. F. L. writes: I first met Hughie Morris when we were both on the staff of the Manchester Victoria Memorial Jewish Hospital in the early 1930's. This professional association grew into a friendship which became very close during the last few years of his life. The courage and patience with which he bore his long terminal illness acted as an inspiration to his friends. I recall one incident when I was looking after him professionally some years ago. I had moved my consulting-rooms from the centre of the city to a point nearer the hospital, and on his second visit I saw a little lubricating-can poking out from his pocket. I thought this an unusual instrument even for Hughie to carry about with him, and so I asked him what it meant. Apparently, on his first visit, he noticed that the hinges of the gate leading to my consulting-room were stiff and squeaky, and he had brought the oil-can to remedy this. That was typical of the many kindnesses he did with self-effacing modesty. We shall miss his skill and we shall miss his happy fun, but the memory of his character and his courage will remain with us.

V. T. THIERENS, M.B., Ch.B., D.P.H.

Dr. V. T. Thierens, formerly medical officer of health for the county borough of Blackburn, died on October 28. He was 65 years of age.

Vincent Thomas Thierens was born at Burscough, Lancashire, on June 22, 1894, and was educated at Stonyhurst College and at Liverpool University. His university training was interrupted in 1914 by war service with the Liverpool Scottish and the Prince of Wales's Volunteers. He fought on the Somme, at Passchendaele, and at Cambrai, where he suffered severe wounds and was taken prisoner. On his return he took up his medical studies again at Liverpool, graduating M.B., Ch.B., with honours in public health, in 1922, and he took the Cambridge D.P.H. in 1924. His public-health career started at Bradford, first as assistant, and later as deputy medical officer of health. In 1928 he was appointed medical officer of health for Blackburn county borough, from which post he retired in June last.

J. Q. M. writes: Dr. V. T. Thierens had the qualities of a leader, a tremendous enthusiasm in all he did, and a remarkable instinct for the right moment to chide or to encourage his colleagues. Although Blackburn is one of the smaller county boroughs, a surprising number of seniors in the public-health world had, in their earlier days, worked under him there. During his period in office he saw the culmination of the sanitary era, the rise of the personal services, and, finally, the introduction of the National Health Service Act. Far-sighted in his work, he was always willing to cast aside pride in past achievement whenever he believed future needs required it. Years before the National Health Service Act he foresaw that a medium-sized borough alone could never provide facilities for chest surgery, and agreed with the larger county authority that it should take over his tuberculosis scheme, a scheme he had spent many years in building up. He was a Fellow of the Royal Sanitary Institute, being a member of its examiners' board, and a Fellow of the Society of Medical Officers of Health and a past president of the north-western branch. He was appointed to the local hospital management committee, becoming its honorary epidemiological consultant, and he did much work for the railway division of the St. John Ambulance Brigade. He was a great reader, and a member of the Blackburn Antiquarian Society, but his chief interest was his work. He leaves a widow, also a member of the profession, to whom our deepest sympathy must go.

A. D. writes: Vincent T. Thierens did not long survive his retirement from the office of medical officer of health of Blackburn, which he had held with great distinction for some 30 years. He was one of the many Liverpool graduates who have made a career in public health. His first appointment was with the Bradford health department, where his chief was the now veteran Dr. J. J. Buchan. His special interest then was school health work. On his transfer to Blackburn he decided to settle down there instead of using it simply as a stepping-stone for further promotion as so many of his predecessors had done, four of whom became medical officers of health of large counties. He was an active and acceptable member of all the local medical and hospital committees, and had been president of the North-Western Branch of the Society of Medical Officers of Health. He ensured good co-ordination between the various branches of the National Health Service. He was the first to originate the idea that a small county borough could provide a better service for the control of tuberculosis by handing it over to a large and efficient county organization. He put this forward at a luncheon with the present Lord Cohen of Birkenhead and Dr. Lissant Cox, then central tuberculosis officer for

Lancashire, and, despite protests from some of his colleagues that he was "selling the pass," agreement was eventually reached by all concerned and the scheme proved to be entirely satisfactory. Vincent was a staunch friend, and even during his long illness was always optimistic. His widow, Mildred, to whom our sympathy goes, is also medically qualified, and is a daughter of the late Dr. W. T. Clegg, a well-known Liverpool ophthalmic surgeon: his brother is a radiologist. Many will remember with affection the warm hospitality of Mowbray Lodge with its delightful occupants, including many friendly dogs.

S. C. G. writes: The death of Vincent Thierens removes from the public-health world one of its prominent members and a colourful personality. It was not in Blackburn alone, however, that he was liked and respected; he was a popular figure among people in all walks of life in Lancashire, and nowhere more than among his colleagues in the public health service. He believed firmly in the importance of the contribution which preventive medicine had to offer, and worked hard to secure a proper emphasis in the preventive service in the developments which followed upon the inception of the National Health Service. His membership of many advisory and co-ordinating committees was an indication of the esteem in which his counsel was held: but he possessed also personal qualities which ensured for him attention and respect.

In day-to-day problems Thierens believed in the personal approach and in the importance of mutual regard and understanding. He was direct and outspoken, but kindly and sincere, and he greatly valued in others that courtesy which he himself invariably displayed. Despite a considerable degree of deafness, he was a most sociable person and loved meeting people. A witty raconteur, he had a great sense of humour and was never short of an amusing story. One was always happy to see him, and he left one feeling the better for having met him. When, towards the end of his active career, illness overtook him, his friends were saddened and dismayed. The courage with which he faced up to the prospect of formidable operative procedures, and his wonderful recuperative powers, gave many cause to hope that he might yet enjoy the long and active retirement which he had so richly merited. It was not to be. Throughout a long and distressing illness, supported constantly by his wife, to whom he was devoted, he displayed the utmost fortitude. The profession mourns the passing of a greatly respected colleague, and sympathy goes out to his widow, Dr. Mildred Thierens, in her irreparable loss.

NORMAN MACFADYEN, M.B., D.P.H.

Dr. Norman Macfadyen, the first resident doctor in Letchworth, and the town's first medical officer of health, died at the Lister Hospital, Hitchin, on June 5. He was 82 years of age.

Norman Macfadyen was born in Manchester on May 21, 1877, the son of a distinguished Congregational minister. He received his medical education at St. Bartholomew's Hospital, and qualified M.R.C.S., L.R.C.P. in 1902. He took the London M.B. in 1904 and the Cambridge D.P.H. in the following year. After qualification he held the appointments of house-physician and extern midwifery assistant at St. Bartholomew's and assistant medical officer at the London Temperance Hospital. He then settled in practice at Letchworth, where he remained for the rest of his life. He was chairman of the executive committee of the Town and Country Planning Association from 1929 to 1944, and in 1945 became the fourth recipient of the Howard memorial medal awarded by that association. He was also chairman of the East Hertfordshire Division of the British Medical Association from 1924 to 1927.

We are indebted to Dr. C. P. CRAGGS for the following appreciation:

Dr. Norman Macfadyen, senior partner and founder of the first practice in Letchworth, the first garden city, died on June 5 following an accidental fall on May 13 which caused a fracture of the neck of his left femur. A kindly and yet forceful man, he and his wife Gertrude made Letchworth their enthusiastic hobby: indeed, being childless, everyone thought of Letchworth as the offspring of the Macfadyens. His wife, who predeceased him in August, 1958, gave striking evidence of this by her gift to the town of nearly £30,000. Notwithstanding this most generous gift, Dr. Macfadyen left almost his entire estate to the Letchworth Civic Trust, which can thus benefit worthy causes in the town and help people in need. After leaving St. Bartholomew's Hospital Dr. Macfadyen came under the influence of Sir Ebenezer Howard, and was one of the first householders in the new garden city at Letchworth, when every visit was difficult owing to primitive road conditions. By the end of 1911 he had been joined not only by Dr. H. D. Ledward (in 1906) but also by Dr. P. F. Wilson, both from St. Bartholomew's Hospital. It was largely owing to the energetic drive of Dr. Macfadyen that Letchworth Hospital was built, and he was, from first to last, medical officer of Letchworth and North Hertfordshire Isolation Hospital, where he successfully treated thousands of children suffering from diphtheria and scarlet fever in the days before prophylaxis and antibiotics were in common use. Both his partners volunteered for active service in the first world war, so that he was left to hold the fort in this quickly growing town as best he might.

I first met Dr. and Mrs. Macfadyen in 1927, and it was their charm and enthusiasm which caused me to decide to settle in Letchworth. "Ours is a very interesting and comprehensive practice, with a small general hospital, an isolation hospital, a tuberculosis dispensary and school medical service, in addition to the routine work." These were Dr. Macfadyen's written words to me when replying to my letter of application to join the practice. I soon found them to be very true, thus making the life of a small-town family doctor one of great interest and variety. We were a large partnership of six. Later we separated from the partners in the neighbouring town of Baldock, but continued to remain in close friendship. I can now look back on over thirty years of friendship and comradeship with my late senior partner, who never failed to give us excellent advice and real guidance in all our problems. His work for the Letchworth Urban District Council, of which he was chairman for many years, was self-sacrificing and distinguished. He was a director of the First Garden City, Ltd., and he gave his services freely to all the young people's and sports organizations. His greatest joy was to be among children, and he and his wife regularly visited all the schools of a wide area. He and his wife loved Letchworth, and gave their all to its service, both during and after their lives. They will not be forgotten; their monument, not of stone, will help the future of their town. As one of his colleagues said, "Never has one man done so much for so little reward."

ADAM MOSS, M.D.

Dr. Adam Moss, who was in general practice at West Kirby, Cheshire, for very many years, died at Firgrove, Cape Province, South Africa, on September 22. He was 90 years of age.

Adam Moss was born on October 21, 1868, and was educated at the old Queen's College, Belfast, graduating M.B., B.Ch. from the former Royal University of Ireland in 1892. He proceeded to the M.D. in 1905. While at the District Lunatic Asylum at Belfast he gained the first prize in mental diseases and the Malcolm exhibition at the Royal Hospital. He first entered general practice at Tyldesley and Boothstown, Lancashire, in 1893, but left there two years later for West Kirby. His initial stay at West Kirby was of short duration, for in 1897 he went to South Africa to take up an appointment as district surgeon at Ladismith, in the Cape Province. In 1901 he returned to West Kirby and to general practice and remained there until 1953,

when he went back to South Africa to live with his son at Firgrove.

A. G. B. writes: For a few years at the turn of the century Dr. Adam Moss practised at Ladismith, Cape Province, and in this short period made a profound impression on the inhabitants of the town. Even to-day, after the lapse of sixty years, there are old people who remember him with respect and affection. In 1901 he returned to his native land and fifty years later was still in active general practice in West Kirby, Cheshire. It was my very great privilege to get to know Dr. Moss on his first return visit to South Africa in 1948. I was deeply impressed by his lovable personality, his serenity and wisdom, and the radiation of his essential goodness. Though I never saw him at work I could well imagine him as the perfect family doctor—a true friend and guide to the many thousands he served during his long life.

E. S. A. A. writes: As a doctor, as a man, and as a friend, Adam Moss stood out in his integrity. Abounding in human sympathy, drawing his strength from hidden sources, with a kindly approach and cheery word, he brought hope and comfort to his many patients. He was twice married, both his wives predeceasing him.

C. D. GUN-MUNRO, M.R.C.S., L.R.C.P., D.O.M.S.

Dr. C. D. Gun-Munro, who was in practice as an ophthalmologist at St. George's, Grenada, British West Indies, died at the Colony Hospital there in September. He was 56 years of age.

Cecil Douglas Gun-Munro was born in Grenada on August 25, 1903. Gaining an Island scholarship in 1922, he then came to England to enrol as a medical student at King's College, London. He qualified M.R.C.S., L.R.C.P. in 1927. He was in general practice in Manchester until 1931, and then in London and Surrey until he entered the R.A.M.C. in 1941 for service in the second world war. Attaining the rank of captain, he served until 1945. Obtaining the D.O.M.S. of the English Royal Colleges in 1946, he then returned to Grenada, where, in recent years, he was senior medical officer as well as ophthalmic surgeon to various institutions. He was honorary assistant secretary of the Grenada Branch of the British Medical Association from 1956 to 1958 and honorary secretary in 1958–9. He came to England to represent his Branch at the Annual Meeting of the Association at Harrogate in 1949 and again at Brighton in 1956. An enthusiastic games-player, Dr. Gun-Munro was a member of the King's College Hospital eleven which won the junior inter-hospitals cricket cup in 1924. In the same year he helped the hospital to win the senior inter-hospitals lawn-tennis cup, the first occasion on which King's had gained the trophy. He later represented Grenada at lawn-tennis. His death is a severe blow to his many patients, to whom he brought comfort in their distress and encouragement through his genial personality. He leaves a widow, two daughters, and one son. His brother, Dr. S. D. Gun-Munro, is in medical practice in St. Vincent, and one of his four sisters is the wife of Dr. W. F. Kerr, of Barbados.

C. J. MORGAN, M.B., B.S.

Dr. C. J. Morgan, who was in general practice at Conway, Caernarvonshire, died at Hammersmith Hospital on October 3. He was 35 years of age.

Cliffard Jones Morgan was born on May 18, 1924, the son of the late Councillor J. R. Morgan, of Llandudno. He was one of a family of four boys, the eldest of whom is a Doctor of Philosophy in the University of Liverpool, and the other two are members of the medical profession in Anglesey and Cheshire. He was educated at the John Bright Grammar School, Llandudno, and studied medicine at St. Bartholomew's Hospital, graduating M.B., B.S. from London University in 1947. After graduation he held the appointment of senior house-physician to the medical professorial unit at St. Bartholomew's Hospital and house-surgeon at the Caernarvon and Anglesey General Hospital, Bangor. He then entered the Royal Air Force for his two years' National Service, attaining the rank of squadron leader. After demobilization he entered general practice, first at Blaenau-Festiniog and, since 1953, at Conway.

T. V. T. writes: Cliffard Morgan's quality was outstanding. He was a man wholly dedicated to his work, and his enthusiasm, sincerity, and winsome disposition earned him immediate friends in all walks of life. He was a friend of consultants and general practitioners alike, and all who knew him respected his convictions and steadfastness of purpose. To work with he was a delightful and an inspiring colleague. A clinical assistant for eight years at Llandudno General Hospital, he was also a police surgeon and medical officer to a large factory. He was a member of the north-west faculty board of the College of General Practitioners, and a founder-member of the Conway and District Medical Society. He was keenly interested in the Toc H movement, and a man of strong Christian conviction. In so short a span he had already achieved much. His early death is a great loss to the community, and medicine in North Wales will be the poorer for his passing. Our sympathy goes out to his widow and young daughter.

D. H. writes: Cliff Morgan had the rare gift of always being more interested in other people than he was in himself. For some years he knew that his time was running out, so he lived it fully in the interests of his patients, his family, and his many friends. His was a rare courage that could see humour even in his own most personal adversity. One left his sickroom feeling strengthened, never depressed, although one felt the end must be very near. To have known him was one of life's rare privileges.

R. J. O. TAYLOR, M.B., Ch.B., D.P.H.

Dr. R. J. O. Taylor, physician-superintendent of the Derwent Hospital, Derby, and Draycott Hospital, Derbyshire, died at his home at Derby on October 6. He was 64 years of age.

Richard James Ogilvie Taylor was born at West Calder, Midlothian, on January 11, 1895, and was educated at George Watson's College and at Edinburgh University, where he obtained his blue for association football. He served as a combatant officer in the Royal Scots during the first world war, and experienced much hard fighting. He graduated M.B., Ch.B. in 1921, and took the D.P.H. of the Scottish Royal corporations in the following year. Subsequently he took up a post as resident medical officer of Wandle Valley Joint Isolation Hospital, later becoming assistant medical officer and bacteriologist to the urban districts of Mitcham, Coulsdon, and Purley. In 1925 he was appointed medical superintendent of Derby Borough Isolation Hospital and Sanatorium, as the Derwent Hospital was then known. He continued as physician-superintendent when the hospital came under the jurisdiction of the Sheffield Regional Hospital Board, and at this time also took up a new appointment as physician-superintendent of Draycott Hospital. He was a member of the Derby Medical Society, a former member of the Medical Superintendents' Society, and an examiner to the General Nursing Council.

R. G. C. writes: Richard Taylor was unassuming in character and of great personal charm and integrity. He was a man of great strength of character and was universally respected by colleagues, friends, and patients. He came to Derby to take over a hospital in the early stages of development, and saw it grow into an efficient institution dealing with many varieties of patient, and this was largely owing to his own ability, enthusiasm, and inspiration. In the same way, he was largely responsible for the conversion and building up of the small isolation hospital at Draycott into a pleasant, well-run hospital for tuberculosis patients. He

was expecting to retire in three months' time to the London he loved, but unfortunately coronary thrombosis supervened. His death is a great loss to his friends, his profession, and the community he served so well. To his widow and his son, Dr. Ian O. Taylor, an assistant medical officer with the Middlesex County Council, must be extended the deepest sympathy in their loss.

H. V. MITCHELL, M.R.C.S., L.R.C.P.

Dr. H. V. Mitchell, who was in general practice at Bournemouth for many years, died at his home at Southbourne on October 11. He was 78 years of age.

Howard Vincent Mitchell was born on March 14, 1881, and was educated at Glasgow University, receiving his clinical training at Guy's Hospital. He qualified M.R.C.S., L.R.C.P. in 1906, and then held the appointment of clinical assistant at Guy's Hospital before entering general practice at Tamworth, Staffordshire, in the following year. From 1909 to 1916 he was in partnership at Clacton-on-Sea, where he was also medical officer to the Reckitt convalescent home of the old Great Northern Hospital. Moving to Stowmarket, in Suffolk, in 1916, he was in practice there until 1923, being also district medical officer for the Hartismere union. He served as a captain in the R.A.M.C. during the first world war. He finally settled at Bournemouth in 1923, and remained there until his death. He leaves a widow, a daughter, and two sons.

P. P. McK. writes: By the death of Dr. H. V. Mitchell Bournemouth has lost a devoted member of the medical profession. Throughout his long medical career his interest in his profession never lagged. His helpfulness and friendliness towards his colleagues, and his unfailing kindness towards, and consideration for, those sick and in trouble greatly endeared him to all privileged to come into contact with him. His passing will indeed be greatly mourned.

J. S. McCOMBE, D.S.O., M.B., B.Ch.

Brigadier J. S. McCombe, formerly deputy director of medical services in the Malta Command, died at his home in Dublin on October 19. He was 74 years of age.

John Smith McCombe was born on April 9, 1885, and was educated at the old Queen's College, Belfast, graduating M.B., B.Ch. from the former Royal University of Ireland in 1907. Entering the R.A.M.C. as a lieutenant in 1908 by passing the competitive professional examination, he was promoted captain in 1911, major in 1920, lieutenant-colonel in 1933, and colonel in 1937. He served in India from 1910 to 1914, and, during the first world war, in Mesopotamia from 1914 to 1917. For the last twelve months of his service in Mesopotamia he was deputy assistant director of medical services of a base force. In 1917–18 he was stationed at Army Headquarters in India, and in 1919 at York in the Northern Command. Subsequent appointments included those of assistant director of medical services, Southern Command, in 1933–4 and deputy director of medical services, Malta Command, from 1937 to 1942. Although due to retire in 1941, he was re-employed and did not leave the Army Medical Services until 1944, when he was granted the rank of brigadier. A man of exceptional courage and endurance, McCombe displayed these fine qualities on more than one occasion. Soon after joining the R.A.M.C. in 1908 he was awarded the Royal Humane Society's certificate and Arnott memorial medal for life-saving; in 1916 the society's bronze medal, again for life-saving; and while in Mesopotamia in 1917 the D.S.O. for bravery in the field. In 1910 he reached the semi-final of the Army and Navy boxing championship as a heavy-weight. His interest in the R.A.M.C. was lifelong, and he purchased the Hale V.C. and other medals and presented them to the headquarters mess of the Corps at Millbank. He was twice married: first, in 1919, to Mrs. Doris Leach, who died in 1946, and, secondly, in 1951, to Joyce, widow of the sixth Baron Talbot de Malahide.

BERYL SUCHETT-KAYE, M.R.C.S., L.R.C.P.

Dr. Beryl Suchett-Kaye died at St. Charles' Hospital, London, on October 11 at the age of 45.

Beryl Daphne White was born on July 7, 1914, and was educated at St. Paul's Girls' School and at the Royal Free Hospital for Women. After qualifying M.R.C.S., L.R.C.P. in 1942 she held the appointments of house-surgeon, house-physician, and resident anaesthetist at the Kent and Sussex Hospital, Tunbridge Wells, and resident medical officer at the Exeter City Hospital. During the second world war she saw active service in Belgium and France, and in after-years looked back with pride and affection to the time she was attached to the Black Watch regiment in Germany. After the war she became senior registrar in anaesthetics at St. Charles' Hospital. Dr. White married Dr. A. I. Suchett-Kaye in 1948, and soon after started a private practice, which, but for her health, would have met with the success she so richly deserved. She was a woman of kindly nature, quiet and unassuming. She took a keen interest in those with whom she worked. A reliable and skilful anaesthetist, she developed a special interest in the field of chest surgery. Her married life was happy, and our sympathy is extended to her husband and four sons.

C. M. R. writes: Dr. Beryl White is deeply mourned by her many friends at St. Charles' Hospital, with which she had had a long association. It was a privilege to have had her as a colleague. Her calm and skill helped many a patient and surgeon, and this same efficiency was seen in her home life. It is sad to lose one so youthful and vital.

ARCHIBALD PENMAN, M.D., D.P.H.

Dr. Archibald Penman, medical officer of health for the Doncaster rural and the Tickhill urban districts, and divisional medical officer under the West Riding County Council, died suddenly on October 17. He was 58 years of age.

Archibald Penman was born on March 8, 1901, and was educated at Edinburgh University, where he graduated M.B., Ch.B. in 1923, proceeding to the M.D., with commendation, in 1937. He took the D.P.H. of the Scottish royal corporations in 1924. Practically all his professional life was spent in the public health service. From 1925 to 1927 he was medical officer of health for Stirling and visiting physician to the Stirling combined fever and smallpox hospital, and from 1927 to 1935 he was assistant county medical officer of health for Hereford. In 1935 he was appointed medical officer of health for the Doncaster rural district and medical officer to the Sprotborough child-welfare centre, and these duties he retained when, in 1947, he became one of the first divisional medical officers in the West Riding. He had the most extensive knowledge of his division, with its many problems, and underneath a humorous approach he had a keen, shrewd, and active intellect. He was a Fellow of the Society of Medical Officers of Health and a member of the Doncaster Medical Society. His untimely death is greatly felt by his colleagues in public health in the West Riding. He leaves a widow, to whom our sympathy is extended.

J. F. writes: With the death of Dr. Archibald Penman, south Yorkshire medical officers of health have lost a most able, well-informed, and pleasant colleague. He was particularly interested in the care and aftercare of patients suffering from tuberculosis, and was for many years chairman of a voluntary committee which did excellent work under his direction. Of unfailing good humour, "Archie" Penman's activities were limited in his later years by failing health, but he was always willing to discuss difficulties with his colleagues and had a very wide and varied experience of public-health activities in rural communities.

HEALTH CENTER LIBRARY

Medical Notes in Parliament

OVER £6M. MORE FOR HOSPITAL BUILDING

The expanded programme of hospital building which the Government envisages provides for a capital expenditure of £31m. in 1961–2 for England and Wales, £5½m. more than in 1960–1. In Scotland the capital expenditure will be some £3,200,000 in 1960–1 and £3,900,000 one year after.

Mr. D. WALKER-SMITH, announcing these figures in a written reply on November 16, said he had asked hospital boards to complete the planning of a number of additional major projects. These include, in the sphere of new building, the start of a new St. Mary's maternity hospital in Manchester and a new mental deficiency hospital in Northamptonshire, and further substantial phases of the new Cambridge teaching hospital, West Wales General Hospital, and Peterborough Hospital.

Large extensions proposed for existing general hospitals include a new medical block at the West Middlesex Hospital; maternity departments at the North Middlesex Hospital and at the City General Hospital, Stoke-on-Trent; and a new surgical block at the Royal Gwent Hospital, Newport. New operating theatres and a physiotherapy department are to be provided at St. James's Hospital, Leeds, and new operating theatres at the London Hospital. There will be additions or improvements at the Westminster Hospital; the Royal South Hants Hospital, Southampton; Leicester General Hospital; Torbay Hospital; and the General Hospital, Birmingham.

New out-patient departments are to be provided for University College Hospital and the Bristol Royal Infirmary. An out-patient department at Walton Hospital, Liverpool, included in the programme will be designed by the Ministry's Design Unit as the first of a number of development projects which will embody and demonstrate the Ministry's views on the design of hospital buildings and provide information about cost. Provision is also being made for alterations necessary on bringing the Royal Naval Hospital, Chatham, into civilian use when its use by the Royal Navy ceases in 1961.

Mental Health Departments

There are a number of large projects in mental health. They include a new psychiatric unit at Darlington Memorial Hospital; the first phase of a unit for longer-stay mentally ill patients at Crookhill Hall, near Doncaster; and additions or improvements to the Northgate (Morpeth), Royal Earlswood (Redhill), and Coldeast (Southampton) Mental Deficiency Hospitals. Some adaptations of wards and other improvements for the accommodation of severely subnormal children are to be carried out at Queen Mary's Hospital for Children, Carshalton, and a new reception unit, out-patient department, and research and teaching unit provided at the Fountain Hospital, Tooting.

In addition the Minister stated that he was considering various other proposals in regard to the planning of large projects made to him by hospital boards, and he hoped to announce shortly a further list of projects on which planning might now proceed.

Hospitals in Scotland

In Scotland the SECRETARY OF STATE is asking the regional hospital boards to complete plans for the following major projects:

(1) At the Royal Infirmary of Edinburgh, a new out-patient department and casualty accommodation and other specialized facilities. This will be the first stage of the reconstruction of the hospital, and will probably also include some new in-patient accommodation designed to facilitate the next stage of the reconstruction.

(2) At the Western General Hospital, Edinburgh, a new out-patient and casualty department, the first stage in the reconstruction of the old part of this hospital.

(3) At the Western Infirmary, Glasgow, a new out-patient and casualty department, together with in-patient accommodation for casualties and orthopaedic patients. This again is the first stage of a major reconstruction.

(4) At Glasgow Royal Infirmary, new specialized facilities for treatment and research, new accommodation for some of the professorial departments, and a new ophthalmological department.

(5) A new unit at Foresterhill, Aberdeen, beside the existing hospitals there, which will contain mainly additional surgical beds and operating theatres.

He hopes it will be possible to complete the detailed planning of these projects in time for building to start by 1962 or 1963. These projects, he stated, together with the proposed new teaching hospital at Dundee, the plans for which were now being prepared, were designed to provide a radical improvement and extension of the facilities available in the main Scottish teaching hospitals. Other projects in non-teaching hospitals were also being considered.

NEW BILLS IN THE LORDS

Central Control of Radioactive Waste

The Government has introduced in the House of Lords the Radioactive Substances Bill, in which it takes powers to improve control over the disposal of radioactive wastes. The Bill was given a formal first reading on November 12.

The Bill is based substantially on the report of an expert panel appointed by the Radioactive Substances Advisory Committee at the request of the Minister of Housing and Local Government, and presided over by Dr. A. Key, senior chemical inspector at the Ministry. This report, *The Control of Radioactive Wastes*, was published as Cmnd. Paper 884 simultaneously with the Bill. It advocates that responsibility for ensuring the safe disposal of radioactive wastes should rest with a central authority; and the Government's Bill proposes that this central control shall be exercised by the Ministry of Housing and Local Government (and the corresponding department in the Scottish Office).

The Bill introduces two stages of control. Persons who keep or use radioactive materials on premises (defined so as to include any trade, business, profession, or corporate activity), or who operate or provide a service with mobile radioactive apparatus, will be required to register. Establishments of the Atomic Energy Authority, Government departments, and sites licensed under the Nuclear Installations (Licensing and Insurance) Act are exempt from registration. In general it will be illegal to accumulate or dispose of radioactive waste except in accordance with authorizations given by the appropriate Ministers. Some existing temporary controls are to be made permanent.

A National Disposal Service

The Ministers will have power to impose conditions on the use of material, premises, and equipment, to require information about movement, and to create an inspectorate to supervise the operation of the Bill. They will take over most of the powers hitherto exercised by the local authorities; and will have power also to organize a national disposal service—possibly by dumping at sea, or burial at specially selected sites—to handle wastes which cannot be safely dealt with in the areas in which they originate. There is provision in appropriate cases, and subject to considerations of national security, for consultation with

local authorities and the supply of information to them on the whereabouts of radioactive materials and methods of disposal. Registration itself does not give authority to dispose; each undertaking, once registered, must submit its proposals for disposing of radioactive waste and get them authorized. While premises occupied by the Crown are generally exempt from the Bill, National Health Service hospitals will require authorization for the disposal of radioactive waste. Penalties for failure to register or to comply with conditions imposed under the Bill include a maximum fine of £100 or imprisonment up to three months on summary conviction, or up to five years on conviction on indictment.

Hospital, University, and M.R.C. Usage

The report describes the usage of radioactive materials in hospitals, universities, and laboratories of the Medical Research Council as follows:

Radium used at hospitals is normally on hire from the Radiochemical Centre, Amersham, and no waste is produced in its use, although occasionally a source is lost. . . . Radioactive wastes are produced primarily from the use of radionuclides as open sources in cancer treatment, where they have an important but very restricted field, and diagnostically. About 130 hospitals have used radionuclides; the great majority continue to do so and the number is increasing. About 30, accounting for half the total use of radionuclides in hospitals, are situated in London and the others in some 70 communities elsewhere, of which only 8 discharge their sewage to rivers used as drinking-water supplies, while 36 discharge direct to sea or tidal waters.

Gold-198 accounts for more than half the activity, iodine-131 for about a quarter, and sodium-24, phosphorus-32, bromine-82, and potassium-42 for most of the rest. All these are short-lived; some longer-lived nuclides are used but in small amount, e.g., cobalt-60, iron-59, chromium-51. Gold-198 is injected into body cavities and precipitates in the body tissues. Normally very little, e.g., from standardization, washings, and general manipulations, is wasted, but occasionally the whole dose of about 100 millicuries may be wasted, e.g., by accident. Radioiodine, in doses of either 5–10 millicuries for treatment of hyperthyroidism or 100–150 millicuries for treatment of thyroid carcinoma, is taken orally Owing to decay, only about three-quarters is ever excreted, and most of this occurs in the first day. The total amount of activity used in hospitals is about 20 curies monthly and is slowly increasing. We [the Key Committee] estimate that the waste, mainly as liquid, is between a quarter and a third of this, some 80% being iodine-131. Judging from the rate of increase in the last six years, we estimate that the liquid waste may double or treble in the next ten years, i.e., some 10–20 curies of liquid waste will arise monthly at hospitals throughout the country. We consider that the best method of disposal is to the sewer, if necessary after decay storage. The level of activity discharged to the sewers should be limited according to the total outflow of effluent from the hospital. Patients who are given internal doses of radioactive material and who either are not admitted to hospitals or are discharged at the conclusion of treatment adopt ordinary toilet disposal in their own homes. The amount excreted is so small that we consider there is no need for any control.

We have no accurate knowledge or assessment of the activity in solid waste from radionuclide therapy. It is quite small; at one big London hospital it is not more than 10 millicuries per month. It consists of paper, swabs, and glassware; we believe that normally suitable arrangements can be made for its disposal with the ordinary refuse, provided highly contaminated waste, e.g., from mopping-up spills, is stored to allow decay. Short-lived therapeutic residues, such as polythene sheet impregnated with activated phosphorus, could be stored, if necessary, before disposal with the ordinary refuse. A problem will arise, however, with highly active units of cobalt-60 and caesium-137 when they have decayed to levels inconveniently low for their purpose but still considerable. The units are up to 1,000 curies or more, and it is believed that some may be scrapped after two or three half-lives, i.e., after 10 or 15 years in the case of cobalt-60 or about 100 years in the case of caesium-137. It may be possible to re-use these sources for other purposes; the caesium would require chemical processing, but cobalt could be re-irradiated to its previous level or used for a purpose requiring only a lower activity. We believe that the sources should be returned after use to a central agency for re-use or disposal by a national service.

Carcasses of experimental animals which normally contain microcurie amounts of radionuclides present a special problem. Storage is unsatisfactory because unless refrigerated they soon become offensive; disposal by burial suffers from the disadvantage that lower organisms will feed on them and may spread the contamination. Incineration under properly controlled conditions is the most convenient method of disposal.

Universities and Medical Research Council

In 1957 about 110 university laboratories received deliveries of radionuclides, including some solid closed sources of high activity which should present no waste and to which our remarks on caesium-137 are applicable. Most universities use the well-known radionuclides, iodine-131, phosphorus-32, sodium-24, potassium-42, bromine-82, sulphur-35, and gold-198, either in the medical departments or for teaching, but a number of the less-well-known radicnuclides are employed for research purposes. The amounts used vary from a few millicuries a month in the smaller universities to about half a curie a month at those specializing in this type of work. The disposal of liquid and solid radioactive waste is normally no more difficult than in hospitals, and our remarks (above) are generally applicable.

Falling in the same category are 12 laboratories of the Medical Research Council which received deliveries of radionuclides in 1957.

Changes in Population Statistics

The Population (Statistics) Bill, given a second reading in the House of Lords on November 12, makes permanent the provisions of the 1938 Act, as amended, and provides for obtaining information on causes of stillbirths for the whole of Great Britain (instead of solely for Scotland) by means of a certificate from the doctor or midwife stating the cause of death and the estimated duration of pregnancy.

Viscount HAILSHAM, Lord Privy Seal and Minister for Science, said the purposes of the Bill were supported by the Medical Research Council. He explained that the Bill substituted a new schedule for that under the previous Act, giving effect to some detailed changes in the information required. (The new schedule states that on registration of a birth or stillbirth particulars may be required of the age of the mother, the age of the father, and except where the birth is illegitimate the date of marriage, whether the mother had been married previously, and the number of her children by the present husband and any former husband; on the registration of death, whether the deceased was single, married, widowed, or divorced, and the age of the surviving spouse, if any.)

Viscount Hailsham described this as being really no more than a reproduction of the 1938 schedule brought up to date in the light of modern requirements and studies. The most important "novelties" were the requirement that the age of the father should be stated on registration of a birth, and the addition of "divorced" to the existing categories on registration of a death. On the extension of the Scottish practice relating to stillbirths, he said that a number of medical organizations had been consulted and were in general agreement. Information from this register was not open to the public, and was available only at the discretion of the Registrar-General. The information was required because it was considered desirable to obtain more statistical data which could shed more light on the causes of stillbirths. Infant mortality had been declining steadily in recent years, but the decline was largely among children aged between 1 week and 1 year. Mortality in the first week of life had not declined as rapidly, nor had the stillbirth rate shown much variation. The statistics established what at first sight was a close and significant connexion between the causes of infant deaths in the first week and causes of stillbirths.

Why the Father's Age?

Lord TAYLOR was "fascinated" by the inquiry about the age of the father, and wanted to know why it was included. Was there any *a priori* evidence of declining fertility in the male? Viscount HAILSHAM explained that the age of the father was required because medical research was more interested now than previously in human mutations. It was interesting to know whether, or to what extent, the age of the father might affect the rate of mutation, because that enabled one to hazard some kind of opinion about the

effect of radioactivity on human mutations. Although it was bound to take some time to build up any significant statistics about anything so small as the proportion of mutational births, it was a matter now considered sufficiently significant for the question to be asked.

BILLS FROM THE BACK BENCHES

Cleaner Rivers, Office Conditions, and Road Users

The ideas that back-bench M.P.s hope to see carried into law this session have emerged from the ballot which gives 30 of them the chance of starting a Bill on the hazardous road to the statute book. Some of them are ambitious. Mr. R. GRAHAM PAGE (Crosby, Con.) has produced a Road Safety Bill, which has second place on February 5 next, to amend the law relating to highways and road traffic by, among other things, providing tests for drunkenness, amending the law relating to compensation for bodily injury, death, or damage to property, and dealing also with licences, lighting, and insurance. His hopes seem likely to be frustrated, however, by the fact that the first Bill on the day, presented by Mrs. H. THATCHER (Finchley, Con.), will be the Public Bodies (Admission of the Press to Meetings) Bill. The purpose of this is to provide for the admission of Press reporters to the meetings of certain bodies exercising public functions.

There are better prospects for those whose luck gave them the first place on one of the available days. That primacy on the first opportunity, November 27, will give Mr. J. RAMSDEN (Harrogate, Con.) the best prospect of all for his Clean Rivers (Estuaries and Tidal Waters) Bill, by which he proposes to amend the 1951 Rivers (Prevention of Pollution) Act, so as to give river boards powers to deal with new outlets and new discharges of trade or sewage effluent into tidal waters or the sea. First in the list on the second allotted day, December 11, is Mr. R. MARSH (Greenwich, Lab.), whose attempt will be directed to filling, so far as a private member may, the gap left by Government failure so far to adopt the Gowers Committee recommendations for improving the conditions of office workers; his measure is the Offices Bill, to make further and better provisions for health, welfare, and safety in offices.

Near the end of the period, on March 4, will come a group of Bills on closely related subjects. Mr. R. SPEIR (Hexham, Con.), who has the first call, wants to make new provisions to control noise "with a view to its abatement"; the short title is the Noise Abatement Bill. Vice-Admiral J. HUGHES HALLETT (Croydon, North-east, Con.) has next a Road Traffic (Driving of Motor Cycles and Mopeds) Bill, by which he seeks to define different classes of motor-cycles and to prescribe different ages and conditions for licences to drive vehicles of each class. Mr. KNOX CUNNINGHAM (Antrim, South, U.U.) wants to amend the Road Traffic Acts for the benefit of persons who have held driving licences in Northern Ireland.

QUESTIONS IN THE COMMONS

Use of Private Accommodation for Old People

The MINISTER OF HEALTH announced on November 10 that the Government proposed to introduce early legislation empowering the appropriate local authorities to use privately run residential accommodation for old people and to make direct provision for meals. He was answering a question by Miss JOAN VICKERS (Plymouth, Devonport, Nat. Lib. and Con.) asking what were the Government's plans for extending the provision of such accommodation, and he said that the new legislation would be in addition to encouraging the controlled development of these services under existing powers.

Oral Penicillin Tests

Dr. EDITH SUMMERSKILL (Warrington, Lab.) asked the Minister if his attention had been drawn to a public announcement made by certain research laboratories on October 26, in which they claimed to have produced a new penicillin to be administered orally which was twice as effective as penicillin; and if he would cause the most exhaustive tests to be made before a decision was taken to include this substance in *Prescribers' Notes*. Mr. WALKER-SMITH replied that he was aware of this announcement. He understood that the reports of the clinical trials that had been undertaken were not yet available. When they were, he would consider whether there was any helpful information suitable for inclusion in *Prescribers' Notes*.

Universities and Colleges

UNIVERSITY OF OXFORD

On September 21 Dr. G. S. Dawes was appointed representative of the University on the board of governors of Repton School, in the place of Mr. E. A. Greswell, who has resigned, until February, 1961, in the first instance.

In Congregation on October 31 the degree of B.M. was conferred on N. de M. Rudolf.

The Medical Scholarship for 1959 has been awarded to William Michael Wardell (University of Otago and Brasenose College).

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

The following degrees and licences were conferred on October 29:

M.B., B.Ch., B.A.O.—J. Sainsbury.
L.M., L.Ch., L.A.O.—Lola M. Hamilton.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

The following candidates satisfied the Board of Examiners at the Primary examination for the Fellowship of the College in September:

B. M. Barrett, A. D. Bird, T. B. Cartmill, L. J. Caust, J. M. Copeland, T. P. Davis, W. N. Etheridge, J. M. Ham, I. H. Hanan, D. F. Hogg, T. B. Hugh, G. A. Kune, D. R. Marshall, P. J. Millroy, J. B. Morris, K. A. Myers, I. A. Penn, A. W. Searle, J. McK. Watts.

The Gordon Taylor Prize was shared equally by D. F. Hogg and I. A. Penn.

The following candidates satisfied the Board of Examiners at the Primary examination for Fellowship of the Faculty of Anaesthetists of the College in September:

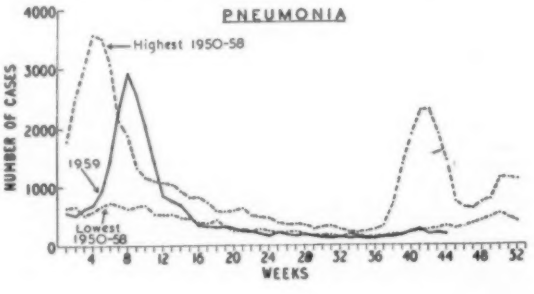
M. J. Bookallil, H. W. K. Chan, J. I. Clayton, Nancye E. Edwards, E. C. Hallett, R. M. Hart, J. Loughman, D. C. Maxwell, N. Potter, B. E. Sharkey.

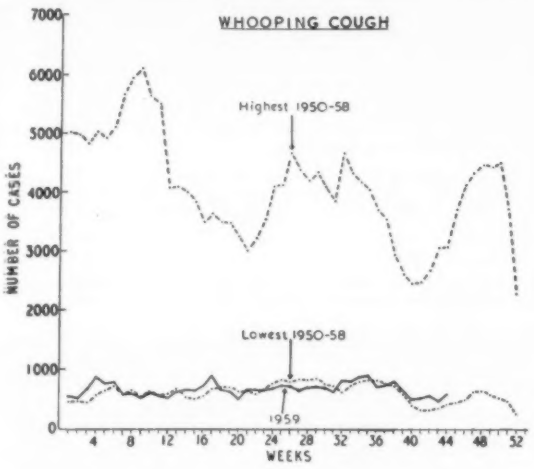
The Renton Prize was shared equally by J. Loughman and B. E. Sharkey.

Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Oct. 31	Week Ending Nov. 7
Dysentery		
Lancashire	138	**123**
Liverpool C.B.	28	**42**
Manchester C.B.	8	**12**
Oldham C.B.	21	**11**
Huyton-with-Roby U.D.	6	**13**
Worsley U.D.	29	**17**
London	41	**45**
Warwickshire	25	**32**
Coventry C.B.	15	**27**
Yorkshire West Riding	74	**96**
Barnsley C.B.	28	**21**
Huddersfield C.B.	21	**23**
Leeds C.B.	13	**19**
Thorne R.D.	6	**14**
Glasgow	120	**104**
Paratyphoid Fever		
Warwickshire	0	**4**
Birmingham C.B.	0	**4**
Lancashire	2	**3**
Manchester C.B.	0	**3**
Continued Fever		
Glasgow	2	**3**
Food-poisoning		
Lancashire	58	**49**
Stretford M.B.	0	**18**
Diphtheria		
Yorkshire East Riding	0	**2**
Kingston-upon-Hull C.B.	0	**2**
Glasgow	2	**4**
Measles		
Northamptonshire	21	**60**
Burton Latimer U.D.	12	**34**
Towcester R.D.	6	**20**
Suffolk	10	**70**
Mildenhall R.D.	1	**28**
Thedwastre R.D.	4	**37**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **October 31** (No. 43) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	2	1	3	0	2	4	3	6	0	2
Dysentery	465	41	208	3	32	525	61	157	5	2
Encephalitis, acute	2	0		0		6	0		0	
Enteric fever:										
Typhoid	5	3	1	1		3	0	0	0	2
Paratyphoid	6	3	0	0	2(B)	10	0	6(B)	0	8(B)
Food-poisoning	195	39	9	0		228	33	15	7	
Infective enteritis or diarrhoea under 2 years				30	38				12	53
Measles*	1,038	15	23	12	31	4,232	243	28	53	205
Meningococcal infection	13	0	11	1	1	29	3	14	0	1
Ophthalmia neonatorum	16	4	4	0		26	4	10	0	
Pneumonia†	207	11	128	3		263	21	164	13	
Poliomyelitis, acute:										
Paralytic	13	3	0	2	2	62	6	26	3	5
Non-paralytic	0	0	0			13	0			
Puerperal fever§	203	26	10	0		212	38	15	1	
Scarlet fever	980	56	125	30	40	803	56	106	27	51
Tuberculosis:										
Respiratory	438	39	73	16		481	58	81	19	
Non-respiratory	54	6	9	6		53	4	8	3	
Whooping-cough	453	30	136	7	47	594	36	69	67	34

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	3	0	2	0	1	6	0	2	1	0
Influenza	16	1	0	0	0	13	3	1	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	369	31	9	14	3	422	28	18	15	3
Poliomyelitis, acute	1	1		0	0	4	1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	49	3	3	0	1	72	5	6	0	5
Non-respiratory		1	2	0	0		0	1	0	1
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	265	26	30	7	17	321	23	26	6	10
Deaths (excluding stillbirths)	8,574	676	527	109	119	9,056	751	539	104	134
LIVE BIRTHS	13,251	1098	957	234	358	13,874	1144	1005	222	344
STILLBIRTHS	240	18	26			307	27	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Queen Mother and Royal College of Physicians, Edinburgh

Her Majesty QUEEN ELIZABETH the Queen Mother dined privately with the President, Dr. A. R. GILCHRIST, and Fellows of the Royal College of Physicians of Edinburgh in their hall on November 7, and was presented with a silver rose bowl to commemorate the occasion. In a brief ceremony after dinner the Queen Mother, who is an Honorary Fellow of the College, signed the promissory obligation and was presented by the President with a copy of the history of the College.

Royal College of Physicians of Edinburgh

At a quarterly meeting held on November 3, the following were elected Fellows of the College:

A. L. AGRANAT, B. BANERJEE, K. S. MATHUR, J. K. DRUMMOND, T. M. WILSON, R. NATARAJAN, J. WILLIAMSON, K. RHANEY, A. B. SCLARE, W. J. WESTON, J. S. MEREDITH, B. E. A. MAGILL, M. F. G. BUCHANAN. M. M. MCLEAN, A. T. DOIG, D. P. BASU, T. J. DANARAJ, A. K. M. MACRAE, P. HARRIS, A. G. FERGUSSON, W. M. JAMIESON, D. J. M. MACKENZIE, D. M. DOUGLAS.

The following were elected Members of the College:

J. D. SUTHERLAND, M. B. MATTHEWS, A. G. BEARN, A. HENDERSON, S. P. GULATI, D. GILL, W. MACKENZIE, J. C. CHATTERJI, F. I. RACKOW, B. MISHRA, N. ROSEDALE, J. L. ELDER, N. S. GHABRA, S. Y. BOKHARI, R. N. GHOSH, B. GUPTA, W. R. PARKES, G. PALMER, G. SUBRAMANIAN, H. D. TOLIA, T. D. BANERJEE, G. Z. COOPER, M. A. SHOKE, R. S. J. SIMPSON, A. H. AKHTAR, K. E. USSHER, A. S. EL HALFAWY, K. R. BALASUBRAMANIAN, A. R. MAY, A. N. MEHROTRA, W. G. WADE, W. D. ALEXANDER, S. C. BOSE, M. A. Z. MOHYDIN, K. R. MITCHELL, F. A. RHODES, R. M. SHAHER, P. P. KENDALL, T. M. CHALMERS, W. HAMILTON, M. B. BHATTACHARYYA, J. D. CORMACK, M. MASUDUZZAMAN, A. K. CHAUDHURI, J. P. INGHAM, R. ST. J. M. BUTLER, K. J. NANAYAKKARA, A. P. SINGH, V. B. GUPTA, I. M. LOWIT. E. R. DAVIES, K. B. MALIK, S. CHANDER, F. T. SAI, D. M. O'SULLIVAN, Y. P. RUDRAPPA, M. S. SABOUR, K. SINGH, T. A. J. DAWSON, J. H. M. LANGLANDS, J. L. JAMES, V. P. GUPTA, R. GAIND, M. BROWN, L. M. BURKE, P. L. DE LA HARPE, S. P. SINGH, L. BRENNER, J. E. THOMPSON, V. J. MARRIAN, S. H. NICOLAIDES, G. R. SUTHERLAND, B. GENTIN, A. K. SAIN, P. D. MARSDEN, A. A. DAWSON, J. B. DAWSON, S. S. NAEEUM-UL-HAMID, C. M. COMTY.

Royal College of Physicians of London

At a quarterly comitia held on October 29 Mr. ISAAC WOLFSON was elected an Honorary Fellow of the College. The president, Sir ROBERT PLATT, announced that the Canadian Government had offered £375,000, which the College has accepted, for the surrender of the lease of their building in Pall Mall East. The College was moving to the Someries site in Regent's Park.

The College has accepted with gratitude a gift of £3,000 from Dr. F. PARKES WEBER to form a trust for promoting advance in dermatology. Dr. DENIS J. WILLIAMS, Dr. G. B. MITCHELL-HEGGS, Dr. C. M. FLETCHER, and Dr. D. V. HUBBLE were elected Councillors of the College; Dr. J. FOREST SMITH was re-elected representative on the Committee of Management. The appointment was confirmed of Dr. HENRY WILSON as College representative on the National Association for Mental Health. The appointment of Dr. H. G. MILLER as Milroy Lecturer for 1961 was announced. His subject will be "Accident Neurosis."

The following were elected Members of the College: A. W. ASSCHER, J. J. BRADLEY, R. B. COLE, J. D. CRAVEN, M. DULAKE, F. ELLIS, Y. E. HSIA, D. T. D. HUGHES, J. M. KENDALL, P. P. KENDALL, H T. R. KOCH, J. G. G. LEDINGHAM, F. I. LEE, A. C. MCDOUGALL, J. M. PARKIN, R. W. PORTAL, E. A. UNDERWOOD, and J. B. WALKER.

Board of Control's Annual Report

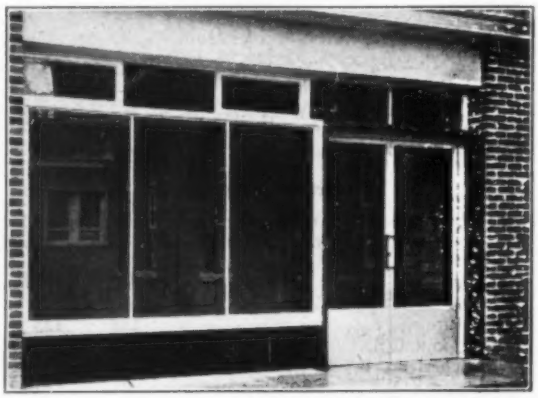
The Board's annual report says that recent encouraging trends have continued (*Annual Report of the Board of Control to the Lord Chancellor for the year 1958*, H.M.S.O., price 9d.).

In particular, there is a steady increase in the number and proportion of voluntary admissions—85% of all admissions, the highest figure yet recorded—and an increasing number of beds to which patients can be admitted without formalities. Moreover, though more patients are being admitted, the number of patients in hospital at any one time is steadily declining, which suggests that more effective methods of treatment are reducing the average length of stay. So far as Broadmoor is concerned, the results of treating chronic psychotic patients there with the newer drugs have been encouraging, though it is still too early to assess long-term results and prospects.

New Portsmouth Radiotherapy Department

A new radiotherapy department at St. Mary's Hospital, Portsmouth, housing an Orbiton cobalt-60 unit and an Eldorado A machine, was opened by Sir STANFORD CADE on October 30.

"Never before," he said, "has any hospital achieved the opening of two cobalt units in one afternoon." Each machine can



[Wright and Logan, Southsea.

treat 25 patients daily, and facilities for 14 in-patients and for out-patients are now available under one roof. The unit, the entrance of which is shown here, was financed by a local appeal which aimed at £12,500 and which raised £33,500 in six months.

Royal Faculty of Physicians and Surgeons, Glasgow

The Maurice Bloch lecture theatre, built with a grant of £20,000 from the Bloch Trust, was opened recently by the donor as an addition to the Royal Faculty building.

The speakers included the President of the Royal Faculty, Mr. A. JACOBS, the Principal of the University, Sir HECTOR HETHERINGTON, and Professor S. ALSTEAD, in whose time as president the building of the lecture theatre began.

Birmingham University

The University's Board of Graduate Studies held a symposium on "Disordered Pulmonary Function" at the Queen Elizabeth Hospital, Birmingham, on October 23 and 24. Over 100 consultants and senior registrars attended.

The chairmen of the three sessions were Professor M. ARNOTT, Dr. B. TAYLOR, and Professor K. W. DONALD. The proceedings will be published in next year's April number of the *British Journal of Diseases of the Chest*.

Lister Memorial Lecture: Duncan, Flockhart Symposium

The sixth Lister Memorial Lecture, under the auspices of the Society of Chemical Industry, "The Chemical Structure and Action of Morphine-like Analgesics and Related Substances," was given in Edinburgh on October 1 by Dr. NATHAN B. EDDY, chief of the section on analgesics, Department of Health, Education, and Welfare, National Institutes of Health, Bethesda, Maryland, U.S.A., and secretary to the National Research Council's Committee on Drug Addiction and Narcotics.

In it he defined the main structural requirements of the morphine-like analgesics, and methods by which greater specificity of action could be secured, and discussed powerful drugs with reduced side-effects which were likely to become available. A symposium, organized by Duncan, Flockhart and Co., Ltd., and covering various aspects of analgesics, was held the next day; two panel discussions were also held on new synthetic pain-relieving drugs and on problems of addiction. It was said that, of 100 cases of "therapeutic" addiction referred to the Ministry of

Health through the Home Office, 55% of the patients were over 60 years old; 35% had been on the drug for three years, 35% for six years, 30% for more than six years; 80% were started on this drug by their general practitioner, 10% by a consultant, and 10% of their own accord. In 75% of these cases there were good medical grounds for starting and continuing the drug.

British Cardiac Society

The Society held its autumn meeting in the Barnes Hall of the Royal Society of Medicine on October 30. Dr. W. PHILLIPS was in the chair. The Society dined together afterwards at the Savoy Hotel, when Sir HENRY DALE, O.M., was guest of honour.

Osler Club Presentation to Dr. W. R. Bett

Dr. W. R. BETT, the secretary of the Osler Club, who has resigned to take up a post in the United States, attended a dinner given in his honour by the club at the Royal College of Surgeons on November 5. He was presented with the *Dictionary of National Biography* and a 1769 Georgian silver tankard.

Esso Refinery's Medical Wing

On November 10 the Esso Petroleum Company's enlarged and re-equipped medical wing was officially opened at their Fawley refinery.

It provides a medical service for nearly 4,000 employees and for the crews of the oil tankers which unload, at the rate of about 10 a day, at the marine terminal. There are four full-time doctors, and facilities include an operating theatre, *x*-ray room, physiotherapy department, and permanent ward accommodation for 12 patients.

King George's Jubilee Trust

King George's Jubilee Trust, of which Her Majesty The Queen is Patron, is to organize a National Appeal during 1960 on the occasion of its Silver Jubilee. The Trust Fund, which was created for the benefit of the younger generation of the United Kingdom, is used to provide opportunities for the development of body, mind, and character, and to help to lay the foundation of good citizenship. This will be the first time since its foundation that the Trust has made a public appeal. Additional funds are now urgently needed to meet the expanding requirements of its work. Inquiries to the Secretary of the Trust, 166, Piccadilly, London, W.1.

Royal Society Royal Medal

A Royal Society Royal Medal has been awarded to Professor P. B. MEDAWAR, F.R.S., Jodrell professor of zoology and comparative anatomy at University College, University of London, for his contributions in the field of tissue-transplantation immunity and acquired tolerance.

Wound Healing Symposium

A symposium on wound healing sponsored by Smith and Nephew Research, Ltd., was held at the Royal College of Surgeons on November 12 and 13.

Among the subjects discussed were radiation and wound healing; the adhesion of wound dressings; clinical aspects of the treatment of wounds, especially burns; and the difficulties involved in closing large open wounds by grafting.

Mr. H. J. Seddon

The degree of Doctor of the University of Grenoble *honoris causa* has been conferred on Mr. H. J. SEDDON.

Scholarship for Non-smoker

The late Mr. J. W. A. HUNTER has left about £50,000 to Aberdeen University to found a medical scholarship. The recipient, who must not smoke while he holds the scholarship and whose parents and grandparents must have been born in Scotland, will be selected by interview, estimation of character, and general attainments, including athletics. (The *Guardian*, November 13.)

COMING EVENTS

National Fund for Polio Research.—Piano recital in aid of the Fund by IRENE KOHLER, November 22, 3 p.m., Royal Festival Hall, London, S.E.1. H.R.H. THE PRINCESS ALICE, Countess of Athlone, has consented to be present.

Heath Clark Lectures.—A course of four lectures, "Research and the Public Health," by Sir JOHN CHARLES, will be given at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1, 5.30 p.m., November 23, 24, 25, and 26.

Birmingham and Midland Medical Art Society.—Foundation meeting November 24, 8.30 p.m., B.M.A. Birmingham Regional Office, 36, Harborne Road, Edgbaston, Birmingham, 15.

London School of Hygiene and Tropical Medicine Association.—The School Association Dinner will be held at the Waldorf Hotel, London, W.C.2, on Friday, November 27, at 7 for 7.30 p.m. (dinner jackets). Tickets 30s. each, exclusive of drinks but including dancing and light refreshments. Applications to Miss K. M. SHAW at the School.

British Society for Immunology.—Autumn meeting, November 27 and 28, the Wellcome Foundation, 183, Euston Road, London, W.C.1. Symposium: "Persistence of Immunity" (chairman, Dr. C. H. ANDREWES), on Friday from 9.45 a.m.

Hand Surgery.—The Hand Club and the Second Hand Club will hold an open meeting at the Royal College of Surgeons, at 10 a.m. to 4 p.m., November 28. Dr. ERIK MOBERG, Gotenburg, will be among the speakers. Details from Mr. H. GRAHAM STACK, 150, Harley Street, London, W.1.

Cambridge University Postgraduate Medical School: Symposia for Anaesthetists.—The following symposia will be held at the Radiotherapeutic Centre, Addenbrooke's Hospital: November 28, "Anaesthesia for Patients with Respiratory Diseases"; March 5, 1960, "Anaesthesia for the Aged"; May 21, 1960, "Anaesthesia for Patients with Circulatory Disease." Details from the Secretary of the Medical School, Tennis Court Road, Cambridge. Enrolment by November 21.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Heart Journal.—Issued quarterly (£3 annually). The new issue (Vol. 21, No. 4) includes:

THE ELECTROCARDIOGRAM OF CARDIOMYOPATHY. William Evans.
PRÆCORDIAL PULSATIONS IN RELATION TO CARDIAC MOVEMENT AND SOUNDS. Patrick Mounsey.
THE ATRIAL SOUND AND THE ATRIAL COMPONENT OF THE FIRST HEART SOUND. Priscilla Kincaid-Smith and John Barlow.
THE ATRIAL SOUND IN HYPERTENSION AND ISCHAEMIC HEART DISEASE. Priscilla Kincaid-Smith and John Barlow.
PROPERTIES AND BIOLOGICAL BEHAVIOUR OF COOMASSIE BLUE. S. H. Taylor and J. M. Thorp.
CLINICAL APPLICATIONS OF COOMASSIE BLUE. S. H. Taylor and J. P. Shillingford.
A TWIN OSCILLOSCOPIC VECTORCARDIOGRAPH. A. J. V. Cameron, T. D. V. Lawrie, and J. H. Wright.
UNEXPLAINED HEART FAILURE IN THE AGED. G. A. Rose and R. R. Wilson.
RUPTURE OF AORTIC ANEURYSMS INTO THE GUT. G. A. Gresham and H. R. M. Johnson.
THE CARDIOGRAM OF CONGENITAL AND ACQUIRED RIGHT VENTRICULAR HYPERTROPHY. J. F. Goodwin and Z. H. Abdin.
THE PATHOGENESIS OF INFARCTION OF THE RIGHT VENTRICLE. W. G. Wade.
CONGENITAL KINKING OF THE AORTIC ARCH. J. N. Pattinson and R. G. Grainger.
PERFORATION OF THE INTERVENTRICULAR SEPTUM IN MYOCARDIAL INFARCTION. J. M. Swithinbank.
CASE REPORTS:
ENDOCARDIAL FIBRO-ELASTOSIS IN A YOUNG ADULT. R. Mulcahy and R. P. Towers.
DISSECTING ANEURYSM OF AORTA ASSOCIATED WITH GOLDBLATT KIDNEY. G. D. Owen and P. N. Coleman.
JOHN HAY. Maurice Campbell and E. Wyn Jones.
PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY.
ABSTRACTS OF CARDIOLOGY.
INDEX.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription, £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, November 21

COLLEGE OF GENERAL PRACTITIONERS.—At Great Hall, B.M.A. House, Tavistock Square, London, W.C., 11.30 a.m., James Mackenzie Lecture by Dr. J. A. L. Vaughan Jones: The General Practitioner and Industrial Health.

Monday, November 23

GUY'S HOSPITAL.—At Physiology Theatre, 5.15 p.m., endocrine demonstration: Diabetes Insipidus.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Sir John Charles: Research and the Public Health—(I) Semantics of Discovery, re-examined.

MANCHESTER MEDICAL SOCIETY: (1) SECTION OF ODONTOLOGY.—At Lecture Room, Dental Hospital 4.30 for 5 p.m., Dr. W. R. Burston: Role of Facial Orthopaedics in the Early Treatment of Cleft Lip and Palate Conditions. (2) SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Medical School, Manchester University, 8.30 for 9 p.m., Dr. A. Cooke: On Making Mistakes.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. Ackner: Principles of Simple Psychotherapy.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Dr. K. G. Lowe: Some Disorders of Renal Tubular Function.

Tuesday, November 24

COLLEGE OF GENERAL PRACTITIONERS: EAST LONDON FACULTY.—At Anatomy Theatre, London Hospital Medical College, 8.30 p.m., Pfizer Lecture by Dr. A. Stuart Mason: Disorders of Sex.

DUBLIN UNIVERSITY: SCHOOL OF PHYSIC, TRINITY COLLEGE.—At Anatomy Theatre, 4.30 p.m., Frederick Price Lecture by Professor W. Melville Arnott: Respiratory Failure.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 10 a.m., Professor T. N. A. Jeffcoate: Stress Incontinence.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Professor J. M. Cumings: Cerebral Lipidoses.

●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, Ashton Street, 7.30 p.m., Professor A. Wilson: Actions and Uses of Drugs in the Control of Allergic Reactions.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Sir John Charles: Research and the Public Health—(II) Early Research in the Field of Public Health.

MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., University Lecture on the History of Medicine by Professor A. C. P. Campbell: Morgagni.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. E. H. Belcher: Radioisotopes in the Study of Blood Circulation.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Mr. F. A. D'Abreu: Some Aspects of Pancreatic Surgery.

ROYAL STATISTICAL SOCIETY.—At Manson Theatre, London School of Hygiene and Tropical Medicine 5.30 p.m., Mr. R. D. Clarke: Recent Trends in Mortality

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Mr. V. B. Green-Armytage: Repeated Abortion.

Wednesday, November 25

COLLEGE OF GENERAL PRACTITIONERS: NORTHERN HOME COUNTIES FACULTY.—At West Hall, Royal Society of Medicine, 9 p.m., Pfizer Lecture by Professor Ian Aird: A Triple Relationship: Patient, Family Doctor, and Specialist.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Recent Advances in Immunology of Mycotic Infections.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. V. Gibson: Constrictive Pericarditis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. R. C. Higham: Enuresis.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Sir John Charles: Research and the Public Health—(III) Harvest of the Nineteenth Century.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor D. A. K. Black: Gastric and Intestinal Function.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH.—5 p.m., Sydney Watson Smith Lecture by Professor Sheila Sherlock: Hepatic Failure.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. Eileen Ring: Health Education in the Maternal and Child Welfare Services.

ROYAL SOCIETY OF HEALTH.—At National Museum of Wales, Cardiff, 10 a.m., Dr. A. H. Griffiths: Case for Mass Tuberculin Testing of Children by Local Authorities.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Dr. W. K. Stewart: Oedema, Sodium, and Water.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Nurses' Hall West London Hospital, 8.30 p.m., discussion. Dr. W. S. C. Copeman, Dr. Redvers Ironside, Dr. Geoffrey Konstam, and Dr. L. P. E. Laurent: Recent Advances in Medical Treatment.

Thursday, November 26

GROUP FOR REPRESENTATION OF THE VIEWS OF CLINICAL PSYCHIATRISTS.—At Rygate Room, Tavistock House North, Tavistock Square, London, W.C., 5.30 p.m.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. O. L. S. Scott: Erythematosquamous Eruptions.

INSTITUTE OF PSYCHIATRY.—At Maudsley Hospital, 5 p.m., public lecture by Sir Rudolph Peters, F.R.S.: Convulsive Conditions and Enzyme Biochemistry.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Symposium: Antibiotics.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Heath Clark Lecture by Sir John Charles: Research and the Public Health—(IV) Developments and Trends in the Twentieth Century, and the Extension of International Collaboration.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 7.45 for 8 p.m., Dr. V. Keating: Metabolic Reaction to Surgery in Coloured Patients.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. T. Alper, Dr. M. Ebert, and Dr. R. H. Thomlinson: Biological Effects of Radiation.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arris and Gale Lecture by Mr. N. R. Barrett: Some Anatomical and Pathological Considerations Concerning Multiple Hydatid Cysts in the Chest.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Professor D. H. Collins: Dysplasias and False Tumours of Bone

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. Hamilton Paterson: demonstration in neurology.

Friday, November 27

BRISTOL UNIVERSITY MEDICAL STUDENT SOCIETY ("GALENICALS").—At Royal Fort, Bristol University, 5.30 p.m., B.M.A. Lecture by Mr. A. Dickson Wright: Momentous Operations.

DUBLIN UNIVERSITY: TRINITY COLLEGE.—At Anatomy Theatre, 5 p.m., Montgomery Lecture on Ophthalmology by Mr. L. B. Somerville-Large: History of Ophthalmology in Ireland.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. W. N. Goldsmith: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. N. Lloyd Rusby and Mr. T. Holmes Sellors.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. S. E. Birdsall: Diseases of the External Auditory Meatus.

INSTITUTE OF NEUROLOGY.—4.45 p.m., Dr. Marion C. Smith: Neuropathological Material Considered in Relation to Neuroanatomy.

KEIGHLEY AND DISTRICT MEDICAL SOCIETY.—At Victoria Hospital, Keighley, 8.30 p.m., Dr. Reginald W. Tattersall: Clinical Significance of Tiredness.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., Dr. H. C. Churchill-Davidson: Dual Neuromuscular Block in Man.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—6.45 for 7.30 p.m., general meeting. Dr. R. D. Catterall: Collagen Disease and the Chronic Biological False Positive Phenomenon.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. J. H. Peacock: Raynaud's Disease and Acrocyanosis. (2) 4 p.m., Professor J. H. Kellgren: Pain and Disability.

Sunday, November 29

MANCHESTER UNIVERSITY, FACULTY OF MEDICINE AND COLLEGE OF GENERAL PRACTITIONERS: NORTH-WEST ENGLAND FACULTY.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Dr. R. W. Luxton: Advances in Management of Certain Thyroid Disorders.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—R. B. Baird, M.B., Ch.B., M.R.C.P.Ed., C.P.H., Whole-time Consultant Pathologist to the Walsall Group; J. G. Hamilton, M.D., F.R.C.S., M.R.C.P., Part-time Consultant Neurosurgeon to Midland Centre for Neurosurgery; E. W. Price, M.B., B.Chir., F.R.C.S.Ed., D.T.M., Whole-time Consultant Bacteriologist to the Birmingham (Selly Oak) Group. *Corrected announcement*: E. J. Newton, M.B., B.S., F.R.C.S., Part-time Consultant Neurosurgeon to the Stoke-on-Trent Group of Hospitals and the Midland Centre for Neurosurgery.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—W. Davison, M.B., Ch.B., M.R.C.P.Ed., Consultant Physician in Geriatrics for duties in Regional Board Hospitals and the United Cambridge Hospitals; R. C. Roxburgh, M.D., M.R.C.P., D.C.H., Consultant Paediatrician, West Norfolk and North Cambridgeshire Area; J. Wedgwood, M.D., M.R.C.P., Consultant Physician in Geriatrics, West Suffolk Hospital Group; Q. S. Moore, M.B., Ch.B., Radiological Registrar, Norfolk and Norwich Hospital; G. D. Henderson, M.B., Ch.B., Registrar in Obstetrics and Gynaecology, Peterborough Group of Hospitals; P. Rapidis, M.D., Registrar in Psychiatry, St. Andrew's Hospital, Norwich; J. G. Camilleri, M.D., D.A., Anaesthetic Registrar, United Norwich Hospitals; M. H. Kemp, M.B., B.S., Registrar in Ophthalmology, Norfolk and Norwich Hospital.

MANCHESTER REGIONAL HOSPITAL BOARD.—J. P. Smith, M.D., Whole-time or maximum part-time Consultant Pathologist, Christie Hospital and Holt Radium Institute; V. Evans, M.B., B.Ch., D.A., Whole-time Assistant Anaesthetist (S.H.M.O.), North Manchester Group of Hospitals; R. Bliss, M.B., Ch.B., D.A., Whole-time Assistant Anaesthetist (S.H.M.O.), Bolton and District Group of Hospitals; C. S. Hajikakou, M.B., Ch.B., Whole-time Senior Casualty Officer, Rochdale and District Group of Hospitals.

MIDDLESEX HOSPITAL.—W. K. Pallister, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist in the Department of Anaesthetics; H. P. Cook, M.B., B.S., M.D.S., F.D.S. R.C.S., Assistant Dental Surgeon in the Department of Dental Surgery.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—Ann R. Templeton, M.B., Ch.B., Assistant Medical Director, Mass Radiography Services, Devon and Cornwall; S. McC. Cannicott, M.B., B.Chir., D.P.M., Assistant Psychiatrist at Mendip Hospital, Wells.

BIRTHS, MARRIAGES, AND DEATHS

MARRIAGES

Brodie—Hiscock.—On October 28, 1959, at Singapore, James Hurrie Brodie, M.B., Ch.B., D.P.H., Lieutenant-Colonel, R.A.M.C., to Winifred Margaret Hiscock, L.R.C.P.&S.Ed., L.R.F.P.S., D.P.H.

DEATHS

De La Cour.—On October 14, 1959, at Surbiton Hospital, George de la Cour, O.B.E., M.B., B.S., Colonel, late R.A.M.C., retired, of 1, Pine Walk, Surbiton, Surrey, aged 79.

Evans.—On October 16, 1959, Alexa Evans (formerly Mitchell), M.R.C.S., L.R.C.P., of 387, Queen's Road, New Cross Gate, London, S.E., aged 41.

Farrer.—On October 15, 1959, at Troutstream Hall, Rickmansworth, Herts, Ellen Margaret Farrer, M.B., B.S., aged 94.

Fentem.—On October 13, 1959, at his home, 52, Cassiobury Drive, Watford, Herts, Thomas Fentem, M.D.

Harris.—On October 16, 1959, Leslie Price Harris, *M.C.*, M.R.C.S., L.R.C.P., L.D.S., of Old Orchard, Sidmouth, Devon.

Mitchell.—On October 11, 1959, at his home, 22, Heatherlea Road, Southbourne, Bournemouth, Hants, Howard Vincent Mitchell, M.R.C.S., L.R.C.P.

Rastrick.—On October 12, 1959, at 6, Christ Church Road, Epsom, Surrey, Robert Joseph Rastrick, M.R.C.S., L.R.C.P.

Thomson.—On October 13, 1959, at his home, Sunnybank, Knockin, near Oswestry, Salop, James Ford Thomson, M.B., Ch.B., D.P.M., aged 48.

Thomson.—On October 18, 1959, at Bridport Hospital, Dorset, James White Thomson, M.B.E., M.B., Ch.B., D.T.M.&H., of 2, Thistlegate House, Charmouth, Dorset, late of Nigeria, and St. Kitts, British West Indies, aged 77.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Controlling Libido in a Man

Q.—*What is the most effective means of controlling libido in a man aged 40 whose wife's frigidity has proved unamenable to treatment ?*

A.—The fact that this man appears to require drug treatment to control his libido suggests that the latter is unusually strong and might be an important contributory cause of his wife's frigidity. Does he, in the unfortunate circumstances of his marriage, really find it so difficult to exercise continence as to require drugs to help him to do so ? After all, very many perfectly normal married men are separated by their duties, often for prolonged periods, from their wives, and manage without difficulty to control their libido. This aspect is emphasized since there is no satisfactory drug, free from side-effects, for diminishing libido. On the one hand, if sedatives, such as bromides or phenobarbitone, are used, the dose needed to control libido of the proportions with which we appear to be dealing here is almost certain to cause drowsiness. On the other, if oestrogens or progestogens are used, their effectiveness will be accompanied by testicular atrophy and, in the case of oestrogens, by gynaecomastia. If drug treatment is really justifiable, stilboestrol in a dose of 2–5 mg. daily is probably the drug of choice, taking into account its cheapness, effectiveness for the purpose, and absence of mental clouding. Against these desiderata must be set the certainty of testicular atrophy and gynaecomastia (which might be painful), and the possibility of nausea.

Browne's Tubes

Q.—*What is the nature of the liquid used in Browne's tubes for control of sterilization efficiency ?*

A.—The Browne sterilizer control tubes contain essentially a slightly alkaline buffer solution in which is dissolved an organic compound (the compound used depends on the temperature range within which the tube is to work) which liberates acid when the tube is heated to a sufficiently high temperature. The solution thus gradually changes from alkaline to acid as heating continues, and the change is registered by a mixture of indicator-dyes which give the solution a red colour when alkaline, turning to green when sufficiently acid. The reaction is a slow one, so that the change to a "safe" colour requires an adequate time at the temperature appropriate to sterilization, and the rates of change of colour are adjusted to the method of sterilization and material being sterilized, so as to leave an ample margin of safety over the "thermal death point" of tetanus spores as recorded in the elaborate studies of Murray and Headlee.[1]

REFERENCE

1 Murray, T. J., and Headlee, M. R., *J. Infect. Dis.*, 1931, **48**, 436.

Retracted Nipples

Q.—*Is there any treatment for grossly retracted nipples in a woman of 24 ? Is there any evidence of an association between retracted nipples and carcinoma of the breast ?*

A.—Retraction of the nipple, sometimes called indrawn or inverted nipple, may be congenital or acquired. In the former case the title is a misnomer, for the nipple has never been otherwise than buried, and the condition has been attributed to anomalies in the development of the areolar skin musculature. The acquired variety is well recognized as being associated with carcinoma of the breast or, much more rarely, with fat necrosis, tuberculosis, some varieties of chronic mastitis, or following trauma, surgical or other, to the breast.

The case under consideration is clearly congenital and may be inherited. There is no known relationship of this variety to carcinoma ; its chief importance is that it causes difficulty in suckling and may lead to infection of the breast from inability to keep the pit in the skin properly cleaned. Mere muscular retraction, which is very active in some women, must of course be excluded before the diagnosis of organic congenital retraction is confirmed.

For cosmetic and functional reasons plastic operations have been devised[1 2 3] to deal with the condition. For the most part they consist in tightening up the subcutaneous areolar muscular layer after drawing out the nipple. The writer has little experience of these operations, but it would appear from the literature that they are not uniformly successful from the functional point of view. In some instances it has been discovered that the nipple is not just buried but has failed to develop properly (athelia).

REFERENCES

1 Michalek-Grodzki, S., *Bull. Soc. Chirurgiens Paris*, 1936, **28**, 387.
2 Basch, K., *Arch. Gynäk. (Berl.)*, 1893, **44**, 15.
3 Sellheim, H., *Zbl. Gynäk.*, 1917, **41**, 305.

Removing Tartar from Dentures

Q.—*Is strong hydrochloric acid suitable for removing tartar from dentures ?*

A.—It is not a good idea to use strong hydrochloric acid on dentures. To stop deposition of tartar on them it is necessary to have a highly polished surface, and any agent which may interfere with this polish is to be avoided. For this reason not only strong chemical solutions but also abrasive powders and suchlike should not be used. If the denture is heavily encrusted with tartar, it is far better to take it to a dental surgeon and ask him to remove it and repolish the denture. Thereafter a gentle brushing with ordinary soap and water night and morning should keep it free.

C-reactive Protein Test

Q.—*How is the C-reactive protein test done ? How should one interpret the results ?*

A.—C-reactive protein, so called because of its reaction with the somatic C-polysaccharide of the pneumococcus, is best demonstrated by a precipitin reaction with a specific antiserum (C.R.P.A.) prepared in the rabbit.[1] This reagent is now available commercially in this country. The test is very simply performed in a capillary tube, but the reagent is expensive. C-reactive protein is a globulin which is not present in normal serum but appears in response to inflammation or tissue necrosis : its presence is therefore not specific for any particular disease, but it is present in the serum in bacterial infections, acute rheumatic fever, recent myocardial infarction, and widespread malignant disease. It is often found also in rheumatoid arthritis, some virus diseases, and pulmonary tuberculosis, and is often present during pregnancy. It gives similar information to that given by the erythrocyte sedimentation rate, but C.R.P. usually disappears from the serum during the course of rheumatic fever before the erythrocyte sedimentation rate returns to normal.

REFERENCE

1 Yocum, R. S., and Doerner, A. A., *Arch. Intern. Med.*, 1957, **99**, 74.

Antihistamines and Sugar Metabolism

Q.—*Do antihistamines have any effect on sugar metabolism ?*

A.—Antihistamines do not have any direct effect on sugar metabolism. Some of the antihistamine drugs in common use—e.g., tripelennamine—potentiate the action of adrenaline, and since the latter causes a rise in blood sugar, mainly by glycogenolysis in liver and muscle, the antihistamines could effect glucose metabolism in this way. There is, however, no evidence that this occurs in clinical practice.

Cyanocobalamin Not a Tonic

Q.—*Some patients with normal blood counts suffer from debility and depression which is relieved by injections of vitamin B_{12}. What is the role of this vitamin in such cases? Many cases of osteoarthritis also receive benefit from it. Has it an antineuritic action?*

A.—There is no scientific justification whatever for the belief that cyanocobalamin (vitamin B_{12}) has any general tonic or antineuritic therapeutic virtues apart from its specific haematological effect in the treatment of the megaloblastic anaemias, particularly Addisonian pernicious anaemia. A wide range of therapeutic actions, in addition to its effect in the treatment of the megaloblastic anaemias, was likewise frequently attributed to liver extract, with an equal lack of scientific clinical justification.

Uncommon Form of Lymphangitis

Q.—*A young man complained of a tender cord-like swelling beneath the skin covering the lateral chest wall and extending vertically downwards from the anterior part of the axilla to the waistline. It disappeared in about a month. Is this a recognized type of lymphangitis?*

A.—Cord-like subcutaneous structures such as the one described, although not very common, are by no means unknown. They are more frequently found over the chest wall and the arm than elsewhere, and there seems to be little doubt that they are due to thickenings of lymphatic vessels. Chronic tubercular lymphangitis and that of syphilitic origin (the latter sometimes on the penis) were often seen in the past but are now infrequent, and, of course, infiltration of lymphatic vessels with malignant cells, as from the breast, is occasionally palpable. The type under consideration is, however, idiopathic—at least, no cause is discoverable on examination. It has been observed in association with a lymphatic fistula, which seems to indicate that it is a variety of chronic lymphangitis. The course of the condition is usually that described in this case and treatment appears to have little effect, although the writer has not had the opportunity of trying steroid therapy in these cases. In some instances a very thin cotton-like band could be felt for long after the main thickening had subsided.

Salty Taste

Q.—*Could oesophagitis account for a persistent and complete lack of taste for food coupled with a strong, salty taste? No local cause has been found, but the patient—a woman of 79—has a hiatus hernia with free regurgitation which was diagnosed many years ago.*

A.—Oesophagitis would not account for a persistent and complete lack of taste for food, coupled with a strong salty taste. Changes in taste appreciation are not uncommonly found in elderly women, but seldom in men. There is no adequate treatment.

NOTES AND COMMENTS

Diagnosis of Hypoglycaemia.—Drs. WILLIAM GOODDY, VINCENT MARKS, and F. CLIFFORD ROSE (London, W.C.1) write: In your answer to the query, "What are the best methods of diagnosing recurrent attacks of hypoglycaemia causing fainting, etc.? Is the six-hour glucose-tolerance curve diagnostic?" ("Any Questions?" October 3, p. 643), you do not sufficiently emphasize the difference between organic and functional hypoglycaemia. Preoccupation with functional hypoglycaemia and failure to distinguish it from serious organic disease may lead to mismanagement. We wish to point out that organic hypoglycaemia may be the sole initial manifestation not only of islet-cell tumour, but also of disease of the liver, pituitary, or adrenal glands. It is in this organic form that symptoms occur during fasting. Functional (reactive) hypoglycaemia, which is more common and far less serious, does not occur during fasting, but results from a disturbance of glucose dynamics. Although this reactive form may be demonstrated by the six-hour glucose-tolerance curve, this test does not show any constant pattern in hyperinsulinism due to islet-cell tumour, where the curves may be completely flat or frankly diabetic. The glucose-tolerance curve is not of value in establishing the diagnosis of islet-cell tumour and should be discarded in favour of the fasting test. The 24-hour fast advocated in your answer is not enough to exclude hyperinsulinism. It has been our experience at the National Hospital, Queen Square, that hypoglycaemia may develop only after a fast lasting 48 hours. Once the possibility of the potentially fatal condition of hyperinsulinism is suspected, the ability to withstand such a fast, preferably on more than one occasion, should be a minimum requirement before excluding the diagnosis.

OUR EXPERT replies: The answer to the question on hypoglycaemia may be criticized on the grounds of omission, but the letter from Drs. Gooddy, Marks, and Rose seems to me to err in the opposite direction. I imagine the authors wish to stress the point that in suspected cases of hyperinsulinism it may be impossible to exclude this diagnosis without submitting the patient to a 48-hour fast; if they had been contented to do this I would have made no comment. In addition, however, they criticize the six-hour blood-sugar curve on grounds which lead me to believe that they are not well acquainted with this test, in which it is the fasting level and character of the curve during the second three-hour period that are the all-important features. The objection that such curves may be flat or diabetic is irrelevant, as the diabetic character is confined to the first three hours at most, after which they all tend to be flat. Functional hypoglycaemia is the commonest condition from which hyperinsulinism has in practice to be distinguished, and it is wise first to exclude it before subjecting patients to long periods of fasting. For this reason, and because the six-hour curve alone or together with a 24-hour fast will establish the diagnosis in many cases with islet tumours, I am strongly in favour of retaining it in the investigation of spontaneous hypoglycaemia. The statement that the 48-hour fasting test is the minimum requirement for the exclusion of hyperinsulinism is contrary to the view of Breidahl and Rynearson,[1] who showed that nothing less than a fast of 72 hours can be relied upon to exclude the diagnosis. If any such thing as a minimum requirement exists, it seems to me to be the demonstration during a typical attack of a single normal blood sugar.

REFERENCE

[1] Breidahl, H. D., and Rynearson, E. H., *J. Amer. med. Ass.*, 1956, **160**, 198.

Prevention of Seasickness.—Dr. D. N. GOLDING (Dublin) writes: In "Any Questions?" (October 3, p. 644) you advise that hyoscine is to be preferred to the antihistamines in preventing seasickness during a short voyage. I wonder whether the drowsiness often induced by an antihistamine, such as dimenhydrinate, is not to be preferred to the disagreeable mouth dryness which is such a consistent side-effect of hyoscine? Most sea and air travellers express a choice for antihistamine preparations, many insisting that the state of emotional tranquillity induced is an additional advantage, while the anti-nausea effect is almost as marked as that of hyoscine.

OUR EXPERT replies: Some time ago I travelled from Gothenburg to London with a distinguished Swedish physiologist by the Swedish-Lloyd line. The sea was very rough. I took hyoscine; he took an antihistamine. I thoroughly enjoyed the marvellous meal provided for Sunday lunch. He could not face it.

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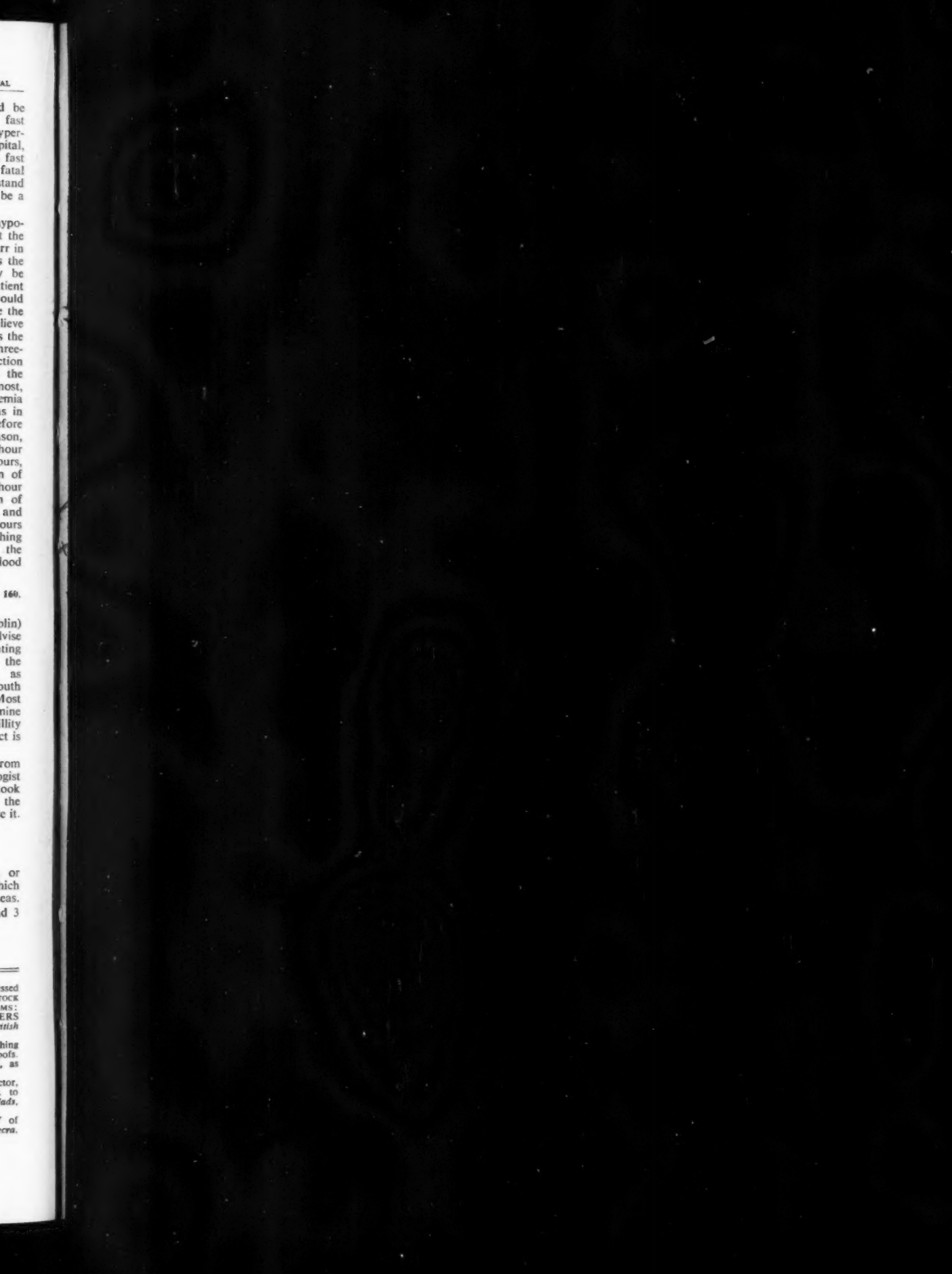
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